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THE PREVENTION OF RESPIRATORY TRACT BACTERIAL INFECTIONS BY SULFADIAZINE PROPHYLAXIS IN THE UNITED STATES NAVY

NAVMED 284

BUREAU OF MEDICINE AND SURGERY
NAVY DEPARTMENT, WASHINGTON, D. C.

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Contents

Introduction

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Experience with streptococcal diseases during 1942-1943 made imperative a program for prevention and control in the Navy. The incidence of scarlet fever, tonsillitis, and pharyngitis was high. Rheumatic fever, with its debilitating sequelae and concomitant disabling effects, increased the alarming loss in manpower and fighting strength. That there was a problem and that action was indicated were indisputable. The opinions as to what should be done, however, varied with the medical officers expressing them, in accordance with the variety of their experiences with streptococcal disease.

On 7 September 1943 a group of medical officers convened at the Bureau of Medicine and Surgery to explore the entire problem thoroughly. These officers were experienced in preventive medicine, both within the Navy and prior to Naval Service, in civilian life. The concensus was that the problem could be attacked from two standpoints, control and study. The prime objective would be to reduce the incidence of streptococcal diseases and consequently the time-loss. Control efforts could certainly be utilized to aid in delineating more clearly the true nature of the problem and point the way to its solution. It was felt that whatever the means of control, it was essential that developments should be kept under scrutiny by trained investigators, to the end that full advantage might be taken of both successes and shortcomings. After a thorough exploration of the means at hand and consideration of the desirability and practicability of the several control studies proposed, the conference concluded that sulfadiazine prophylaxis would provide the most feasible approach and the maximum benefit to the Navy.

Commander Alvin F. Coburn, MC-V(S), U.S.N.R., nationally known authority on streptococcal diseases, was selected to organize the program and to set it in operation. Supplementary to field administration of the project, it was necessary to establish a streptococcal typing laboratory and

to provide adequately trained personnel. Fortunately, Lieutenant Commander Armine T. Wilson, MC-V(S), U.S.N.R., formerly of the Rockefeller Institute, was available for this purpose.

A preliminary survey of six of our larger Naval activities was immemediately undertaken, and arrangements were completed to place the program in operation under supervision of the epidemiology units already assigned. Administrative problems were rapidly solved, and on 15 December 1943 the program was well under way at these major establishments. Programs of less magnitude were authorized from time to time.

The complete story of the sulfadiazine prophylaxis program as it was carried out at each of the Naval activities is presented in the following pages of this monograph, together with a summary of the total program and a consideration of its implications. This project, it is believed, is the largest controlled investigative study ever undertaken and is marked by productive results and guideposts which will surely find their way into the history of preventive medicine. Inevitably, development was troubled by errors, although little time was lost in their correction.

Earnest tribute is due the officers and men and women of the epidemiology units who carried so much of the responsibility of this program. For them a round-the-clock schedule was not too much in order to insure that each patient was fully cared for and that all the investigative elements were fully considered. Their loyalty and interest were exemplary.

Finally, the man who had the courage, the point of view, and the determination to carry on was Vice Admiral Ross T McIntire (MC), U.S.N., Surgeon General of the United States Navy and Chief of the Bureau of Medicine and Surgery. His judicious counsel and encouragement, as well as that of Rear Admiral Luther Sheldon, Jr. (MC), U.S.N., Assistant Chief of the Bureau, supported us steadily in this practical application of preventive medicine.

Report 1

The Grouping and Typing of Beta Hemolytic Streptococci

From the Streptococcus Typing Laboratory, Epidemiology Unit 100 National Naval Medical Center, Bethesda, Md.*

The serologic identification of strains of bacteria is useful in studying the spread of epidemic infectious disease. In the case of beta hemolytic streptococcal infections, the strains are first assigned to the group to which they belong, and if they are members of group A (Lancefield), they are further differentiated according to their types within group A.

When the current sulfadiazine prophylaxis program was initiated in the Navy, a streptococcal typing laboratory was established at the Naval Medical School, National Naval Medical Center, Bethesda, Md., and strains were sent to that laboratory from the various activities participating in the program, for serologic identification. This report presents the basis of serologic grouping and typing and a brief account of the methods employed. The use made of the grouping and typing data supplied by the laboratory is presented in detail in the succeeding reports of this epidemiology symposium.

Grouping

For the purposes of this investigation, interest was restricted to group A beta hemolytic streptococci, because members of that group are responsible for almost all hemolytic streptococcal respiratory illness in man. By means of a potent and specific absorbed group A serum, it was possible to test for membership in group A alone, and, on the basis of reaction or absence of reaction with that serum, to assign a strain to group A, or to say that it did not belong to group A. Strains that were not members of group A were not further identified.

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* Participant: Armine T. Wilson, Lieutenant Commander (MC) USNR.

Assistants: George Prentice, Chief Pharmacist's Mate; Harold Elwyn, PhM1c, USNR; Isabel Erskine, PhM2c, USNR; Hulda Hobbs, PhM2c, USNR.

The Basis of Typing

There are two methods of typing group A streptococci in current use: One is the slide agglutination method of Griffith (*1*); the other is the precipitin technic of Lancefield as modified for use in capillary tubes (*2*). From an epidemiologic point of view, it matters little which method is used to determine the type of strain so long as the same method is used for all the material to be treated in one analysis. It should be understood that the results of the two methods are not always in agreement, because, in certain instances, they measure different antigenic components of the organism.

Hemolytic streptococci of group A have two type-specific antigens, known as M and T. In precipitin typing, only the M antigen or M substance is involved. The M antigen is protein in nature and is extractable from the cell into solution by acid. When such a cell-free extract is neutralized and placed in contact with an anti-M containing serum prepared from a strain of the same type, a precipitin reaction occurs. With serums prepared from other types, no such reaction occurs, provided the serums have had their group and non-type-specific antibodies removed by absorption.

The method of precipitin typing, then, consists of placing an acid extract of an unknown strain in contact with the absorbed anti-M serums of all known types. The type with which the extract reacts will be the type of the strain.

In the intact cell the M substance usually, although not always, participates in an agglutination reaction when a suspension of cells is added to an anti-M containing serum of the same type. The antibodies to the M substance are also responsible for the type-specific immunity that an animal acquires when actively or passively immunized.

The T antigen, on the other hand, has not yet been identified chemically nor can it be demonstrated outside of the cell. Its presence is recognized only by agglutination of the intact cell in the corresponding anti-T serum. So far as is known, it is never involved in a precipitin reaction, and it does not influence the immunity of the animal to infection.

It can be seen that whereas the precipitin typing method depends entirely on the reaction of the M substance of the organism with its corresponding antibodies, the slide agglutination typing method may involve the M substance and its antibody, or the T antigen and its antibody, or both. If particular M and T antigens were invariably associated in particular types, there would be no reason for confusion in the use of the two tests. This, unfortunately, is not the case (*3*). Some strains are without demonstrable M substance, although they contain T antigen, and other strains are without T, although they contain M. Some strains, which share the same M substance and hence will be assigned to the same type on the basis of precipitin typing, have T antigens of different types, and will be

assigned to different types when tested by slide agglutination Other strains with the same or serologically related T antigens have distinct M antigens. One strain has been encountered with the M antigen of one type, a T antigen of the same type, and an additional T antigen of another type.

For a complete antigenic analysis both precipitin and agglutination technics must be employed, serums being used of accurately known antigenic composition. The unusual combinations of antigens mentioned are not frequent, but occur often enough to make it unsafe to compare epidemiologic data based on slide agglutination typing alone with data based on precipitin typing alone, and vice versa. For most epidemiologic purposes, however, a single method will suffice, and the choice of method to be used in any given investigation will depend on the availability of reliable serums and the experience of the typer.

Methods

In this investigation the capillary precipitin method of Swift, Wilson and Lancefield (*2*) has been used exclusively. The details of that method are given in full in their article, and will be reviewed only briefly here. The method was devised in an attempt to make precipitin typing practicable in large-scale typing enterprises, and the essential advantage which it possesses over commonly used precipitin tests lies in the conservation of materials made possible by the use of capillary types in which to develop the reaction. The serums used in capillary typing must be of high potency and specificity, and we were fortunate in obtaining ample supplies of such serums through the generosity of Doctors Homer F. Swift and Rebecca C. Lancefield of the Hospital of the Rockefeller Institute for Medical Research.

Precipitin testing in capillaries is accomplished by drawing a small amount of serum into the capillary tube by capillary attraction, and then drawing an approximately equal amount of extract into the tube, without allowing an air bubble to separate the two liquids. Depending on the strength of the serums used, the precipitate appears immediately, or after 2 hours' incubation at 37° C., or after having been kept overnight in the icebox.

Strains were sent from the field to the Bethesda laboratory as soon as possible after isolation. They were stored in the icebox until ready for study. They were then tested for pure culture and were grown in 40 cc. of tryptose phosphate broth, fortified with 0.5 percent normal horse serum or rabbit serum. The organisms obtained from such cultures were extracted with hydrochloric acid. After the extract was neutralized, it was ready for grouping and typing, the same extract being used for the two procedures.

It was discovered early that most of the strains which were ultimately typed fell into ten common types: 1, 3, 5, 6, 12, 17, 18, 19, 24, and 30. For this reason it was decided to set up the extracts first with these ten serums. If the strain did not belong to one of these types, it was then set up with the other typing serums. At one station (Farragut) the majority of strains belonged to types 1, 17 and 19, and a further reduction in initial typing was possible in that instance. These screening procedures resulted in a significant saving of time, serums, and capillaries.

Serums were available for 36 of the 40 known types of group A beta hemolytic streptococci. In addition to the ten common ones listed, these were 2, 4, 8, 9, 11, 13, 14, 15, 22, 23, 26, 28, 29, 31, 32, 33, 36, 37, 38, 39, 40, 41, 42, 43, 44, and 46.

TABLE 1.—*Serologic types of hemolytic streptococcus at naval training stations*

Type	Bainbridge	Farragut	Great Lakes	Sampson	Other Activities	Total
1	87	108	54	11	34	294
2	4	0	2	3	3	12
3	26	61	72	48	28	235
4	0	2	1	2	0	5
5	28	4	94	29	6	161
6	28	22	23	30	18	121
8	0	1	0	1	3	5
9	0	3	1	1	0	5
11	0	0	0	2	0	2
12	27	7	12	34	10	90
13	1	0	1	3	1	6
14	5	22	0	4	23	54
15	0	0	0	0	0	0
17	69	305	95	26	93	588
18	85	10	1	4	4	104
19	392	342	78	15	128	955
22	0	0	0	0	0	0
23	0	0	0	0	0	0
24	36	25	6	12	6	85
26	0	0	7	7	4	18
28	4	4	0	2	2	12
29	6	0	0	2	0	8
30	30	1	3	21	12	67
31	0	0	0	0	0	0
32	0	0	3	2	0	5
33	2	2	1	2	0	7
36	4	20	6	2	16	48
37	0	0	0	0	0	0
38	0	0	0	0	0	0
39	0	0	3	2	0	5
40	0	0	0	0	0	0
41	3	2	2	9	1	17
42	0	0	0	0	0	0
43	2	0	1	2	0	5
44	2	2	1	3	1	9
46	1	0	1	0	2	4
?	134	111	64	168	87	564
Not group A	258	135	104	394	178	1,069
Total	1,234	1,189	636	841	660	4,560

Results

Table 1 gives an over-all summary of the findings regarding strains on which work was completed by 31 May 1944. It can be seen that slightly more than 20 percent of the strains submitted were not group A strains; 83 percent of the group A strains were successfully typed with the serums available. High proportions of untypable strains were received from the Sampson station and from cultures of a group of healthy carriers at Bainbridge. It is well known that carrier strains are often low in M content; hence they are difficult to type by the precipitin method. It is possible, to be sure, that some of the failures may have arisen from the presence of strains belonging to types for which no serums were available.

The significance of the distribution of types in relation to the epidemiologic conditions in the field is considered in the succeeding reports.

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1. Griffith, F.: Serological classification of streptococcus pyogenes. J. Hyg. **34:** 542-584, December 1934.

2. Swift, H. F.; Wilson, A. T.; and Lancefield, R. C.: Typing group A hemolytic streptococci by M precipitin reactions in capillary pipettes. J. Exper. Med. **78:** 127-133, August 1943.

3. Lancefield, R. C., et al.: Studies on the antigenic composition of group A hemolytic streptococci. J. Exper. Med. **79:** 79-114, January 1944.

Report 2

Mass Administration of Sulfadiazine in the Prevention of Respiratory Illness United States Naval Training Station, Farragut, Idaho

*From Epidemiology Unit 22**

Soon after the commissioning of this station on 15 September 1942 the outstanding epidemiologic fact was the rapid development of a high incidence of respiratory diseases. A high communicable disease incidence among unseasoned recruits of training stations is not unusual. The morbidity rate for respiratory tract infections, notably scarlet fever and other streptococcal diseases, became consistently higher, however, than that of other U. S. Naval Training Stations and persisted throughout 1943. This observation is illustrated in chart 1.

As a result of these infections, severe attacks of rheumatic fever occurred in large numbers of personnel stationed at Farragut during the first year, and the incidence of this disease increased to an alarming degree early in the second year. It was already known that this particular section of the Northwest had for years reported one of the highest per capita rates for acute rheumatic fever among the civilian population; nevertheless, it appeared that factors other than environment were operating among Naval personnel. Among these were the rapid expansion of intensive training programs necessitated by urgent military needs, which took precedence over health precautions and created overcrowding; and a daily influx of raw recruits which constantly furnished new groups of susceptible persons.

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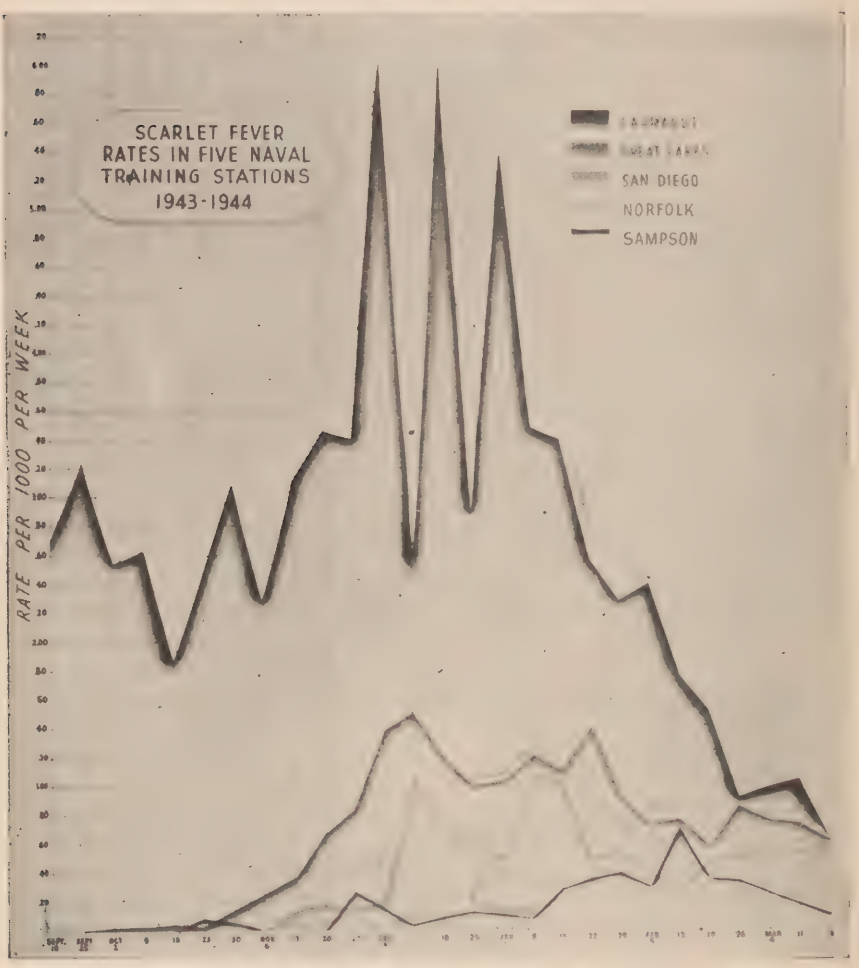
* Participants: Wm. P. Mull, Captain (MC) USN; B. B. Breese, Lieutenant Commander (MC) USNR; A. F. Errington, Lieutenant Commander (MC) USNR; Walter Stoeffler, Lieutenant Commander (MC) USNR; and Grove G. Wiley, Pharmacist USNR.

The following enlisted personnel assisted in the laboratory, field, and analysis of data: Wm. D. Harrison, PhM1c; Edward L. Warmanen, PhM1c; Carl G. Johnson, PhM1c; Louis E. Wagshol, PhM1c; Peter Packet, PhM2c; Alfred H .Rodger, PhM2c; LeRoy V. Grussendorf, PhM2c; Gene W. Johnston, PhM2c; Fred W. Elias, PhM3c.

All approved control measures against communicable disease were observed in so far as possible with facilities available at this station. The initial physical examination of incoming recruits was as thorough and searching in every detail as was consistent with the speed necessary to finish each day's volume. A strict segregation by company was main-

CHART I



tained among all recruits for an initial period of 3 weeks. This assured as nearly an ideal control of communicable disease as was possible without interfering with the normal training program. Despite these precautions, it was soon apparent that the respiratory disease problem presented a challenge, and it was recognized that observance of the principles of preventive medicine had failed to keep respiratory infection rates within reasonable limits. Some form of protection was essential to continue the functioning of this Naval activity as an effective wartime military organization. The situation became urgent.

The daily sick list approached 8 percent of the combined personnel of the station and a large percentage of the ill had severe hemolytic streptococcal infections; furthermore, about 200,000 men were leaving this station annually for other assignments or their homes, and about 30 percent of them were carrying in their throats highly communicable pathogens and virulent strains of hemolytic streptococcus. It was conceivable that millions of streptococcal infections might be disseminated throughout the world.

With a pandemic in the making, a program for the control of streptococcal infections by mass prophylaxis with sulfadiazine was initiated on 5 December 1943. This is a report of various aspects of the Streptococcal Program at Farragut Naval Training Center between December 1943 and April 1944.

History and Methods of Study

Mass sulfadiazine prophylaxis was first instituted in two camps of approximately 5,000 men each: Camp Bennion (C) and Camp Hill (D). Sulfadiazine, 1 gm., was administered daily to each recruit. Camps Waldron (A) and Ward (B) were used as controls. They were equal in size, identical in physical structure, and their personnel were drawn from the same population of incoming recruits as that of Bennion and Hill. Each of the four camps admitted companies of approximately 120 men from the Receiving Unit. These companies were sent in rotation to Camps Waldron (A), Ward (B), Bennion (C), and Hill (D). All recruits in these camps underwent identical training. At first, the program of mass prophylaxis was designed to permit carefully controlled observations. From 5 December 1943 until 7 February 1944 each recruit at Camps Bennion (C) and Hill (D) was maintained on 1 gm. of sulfadiazine daily; whereas recruits at Waldron (A) and Ward (B) received no chemoprophylaxis. Careful clinical and bacteriologic studies were made to determine the effect of the program on respiratory tract infections.

On 17 January 1944 Camp Peterson (E), the Service School group which had had previous recruit training, either at this or some other station, was divided into two groups: Those living in the odd-numbered barracks received 0.5 gm. of sulfadiazine daily and those in even-numbered barracks received none. On 17 January 1944 Camp Scott (F), which was composed largely of special assignment recruits, was similarly divided into two groups: One received sulfadiazine, 0.5 gm. daily; the other group received no prophylaxis. These two camps were treated in this manner for 4 weeks when the entire complement of both camps was placed on a program of sulfadiazine prophylaxis.

On 13 February Camps Waldron (A) and Ward (B), which had served as untreated controls, were each divided into two groups: In each camp the men in odd-numbered companies were given 0.5 gm. of sulfadia-

zine daily and those in even-numbered companies, 1 gm. daily. Clinical and bacteriologic data were collected in these four camps (A, B, E, and F) to determine the effectiveness of 0.5 gm. of sulfadiazine administered daily.

On 13 February, all men in the Out-Going Unit of the station (average 4,000 to 6,000) were given 1 gm. of sulfadiazine daily. Because of the tremendous variation in barracking, messing, and length of time on station, no attempt was made to use this group for controlled study. The duration of their stay in the Unit varied considerably and was frequently more than a month.

On 6 March a daily prophylaxis of 1 gm. was instituted among the station personnel (about 6,000 men). At the same time prophylaxis was made available to officers and civilian employees throughout the station.

In addition to records maintained regarding respiratory morbidity rates in all the treated and control groups, as many as possible of the ill in each group were seen by medical officers of the Epidemiology Unit. Throat cultures were obtained from an appropriate sample of recruits with respiratory infections. Positive cultures were graded from 1 to 4-plus, depending on the heaviness of growth of hemolytic streptococcus. Most of the positive cultures were sent to the National Naval Medical Center for grouping and typing by the Lancefield precipitin method. The results of these examinations were mailed to this station.

Clinical Results

Observations at Farragut.—Mass sulfadiazine prophylaxis at Farragut Training Center was highly successful. This was evident in the first 2 weeks of the controlled study. Admissions for all bacterial infections of the respiratory tract in the two camps receiving prophylaxis dropped precipitously during the first week. Admissions for rheumatic fever dropped strikingly in the second week of prophylaxis. Virus infections were apparently not affected. The data collected prior to and during the first 2 weeks of prophylaxis are presented in table 2.

Successive extensions of the program provided more information. The number of men reporting to sickbay with mild respiratory symptoms which did not require admission progressively decreased. Not only was the total amount of disease markedly lowered in the groups receiving prophylaxis but also the relative importance of the bacterial infections was strikingly reduced in these groups. This is shown in chart 2. The effect of several extensions of sulfadiazine prophylaxis on the scarlet fever rate in January and February is also shown in chart 1.

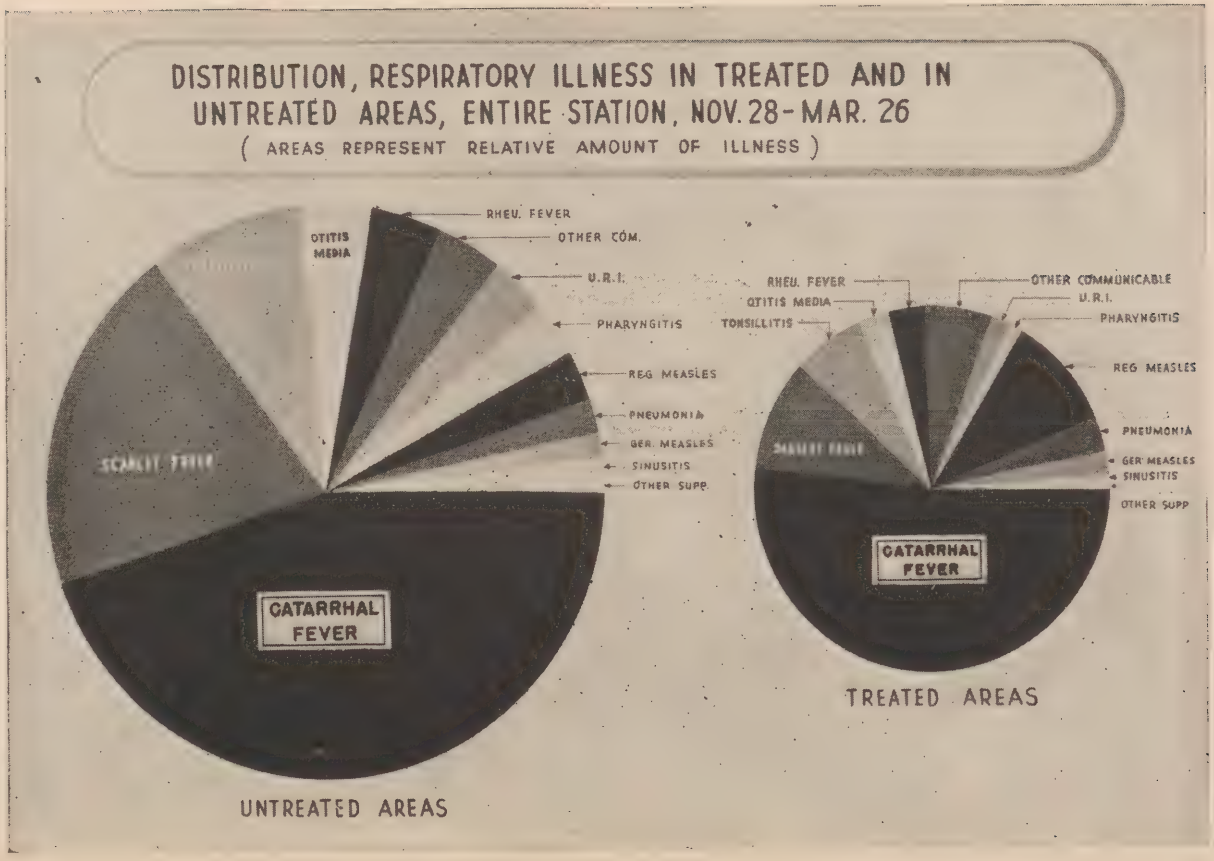
The extension of the program to all enlisted personnel about the first of March eliminated the untreated groups. As a result, controlled observations were no longer possible. We therefore compared the trends during the spring months with trends indicated in Public Health Reports.

TABLE 2.—*Respiratory diseases in four camps prior to and during first 2 weeks of sulfadiazine prophylaxis in Camps C and D*

Diagnosis	Number of cases admitted to hospital and dispensaries													
	Observation period										Inception of prophylaxis period			
	* Nov. 7		Nov. 14		Nov. 21		Nov. 28		Dec. 5		Dec. 12		Dec. 19	
	C.	P.	C.	P.	C.	P.	C.	P.	C.	P.	C.	P.	C.	P.
Scarlet fever	62	57	43	46	68	61	54	53	94	75	81	11	69	14
Tonsillitis	27	40	34	25	46	39	41	34	23	25	21	5	33	4
Pharyngitis	21	6	22	2	26	2	22	7	23	0	4	0	13	3
Catarrhal fever	70	159	79	143	86	171	197	291	248	186	187	72	184	79
Sinusitis	6	4	3	3	0	1	4	2	6	3	3	1	2	0
Otitis media	11	7	6	9	4	5	12	8	11	2	10	1	13	5
Pneumonia (lobar and broncho)	0	0	1	0	1	2	2	6	4	3	2	1	4	0
Meningitis	1	1	0	0	1	1	0	1	0	0	0	0	0	0
Other U. R. I. (bronchitis, laryngitis)	1	1	2	1	2	1	3	0	12	0	12	0	11	1
Rheumatic fever	10	10	12	6	12	6	17	9	7	8	10	10	21	3
German measles	1	0	0	0	2	0	0	0	1	0	1	3	2	2
Measles	1	0	0	0	0	1	0	0	0	4	3	5	4	19
Atypical pneumonia	0	3	0	0	4	2	1	4	1	9	9	3	3	4
Other communicable diseases (mumps, etc.)	2	3	2	2	0	1	10	0	3	1	0	10	14	1
Total—All respiratory infections	213	291	204	237	252	293	363	415	433	316	343	122	373	135

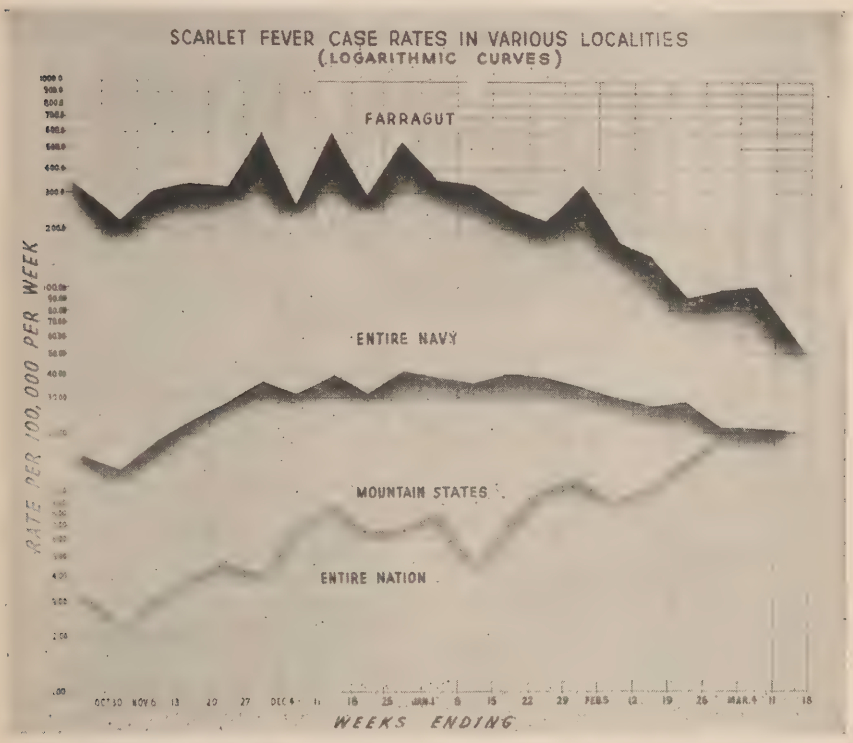
* Week ending.

'C." is Control Group, about 10,000 men. "P." is Group of about 10,000 men who received daily prophylaxis beginning 5 December 1943.


DISTRIBUTION, RESPIRATORY ILLNESS IN TREATED AND IN UNTREATED AREAS, ENTIRE STATION, NOV. 28 - MAR. 26
(AREAS REPRESENT RELATIVE AMOUNT OF ILLNESS)
OTITIS MEDIA
RHEU. FEVER
OTHER COM.
U.R.I.
PHARYNGITIS
REG MEASLES
PNEUMONIA
GER. MEASLES
SINUSITIS
OTHER SUPP.
SCARLET FEVER
CATARRHAL FEVER
UNTREATED AREAS
RHEU. FEVER
OTITIS MEDIA
TONSILLITIS
OTHER COMMUNICABLE
U.R.I.
PHARYNGITIS
REG MEASLES
PNEUMONIA
GER MEASLES
SINUSITIS
OTHER SUPP
SCARLET FEVER
CATARRHAL FEVER
TREATED AREAS

These observations are presented in chart 3. It is seen in this chart that the scarlet fever rate fell during the spring months at Farragut Naval Training Center, which was known to be heavily seeded with highly communicable scarlatinal strains of hemolytic streptococcus and to be receiving a large number of susceptible recruits daily. At the same time it rose in the Mountain States and throughout the United States.

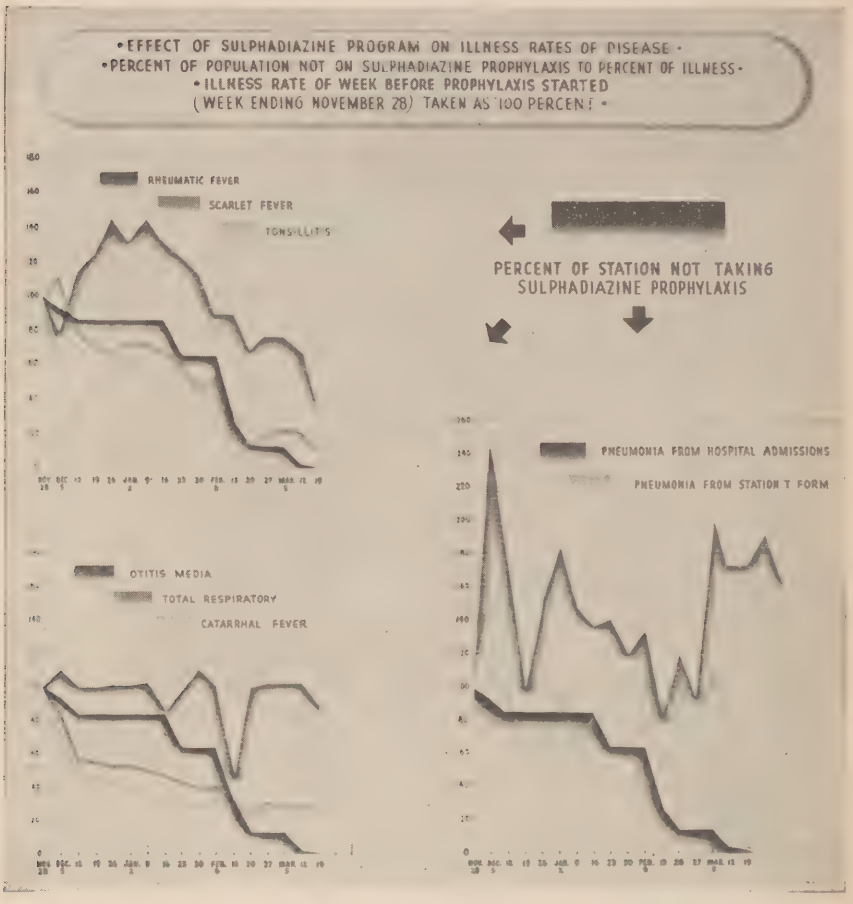
CHART 3



The influences of the extension of prophylaxis on the incidence of various respiratory diseases prevalent at Farragut were determined in the following way: The illness rate for the week preceding the use of sulfadiazine on the station was taken as the base and given the value of 100 percent. At this time the number of men not receiving sulfadiazine was 100 percent. As the number of men receiving the drug increased, the value percent of men not taking sulfadiazine decreased until 6 March when all hands were ordered to take prophylaxis and the percentage fell theoretically to zero. The associated decrease in illness of the more important disease is shown in chart 4. It is seen in this chart that, although most diseases declined as the number of men receiving sulfadiazine decreased, this was not true for pneumonia and otitis media. Subsequent bacteriologic observations indicated that the type of pneumonia did change, however, from one that was was predominantly streptococcal in origin to one that was predominantly pneumococcal.

The number of meningococcal and gonococcal infections was so small on this station that no conclusions can be drawn concerning the effectiveness of sulfadiazine prophylaxis. It is of interest, nevertheless, that in this large, overcrowded training center, meningococcus remained inactive throughout the course of this prophylactic program.

CHART 4



Effect of Sulfadiazine Prophylaxis on Transmission of Streptococcal Infections to Other Environments.—One concern to medical officers at Farragut was the transmission of highly pathogenic strains of hemolytic streptococcus to other Naval activities and to the civilian population. All recruits received 2 weeks' leave following "boot" training, and each week large numbers of men in the Out-Going Unit were detached to other stations. It was disturbing that a large number of men who appeared in good health on departure from Farragut became ill with streptococcal diseases at home, en route, or shortly after arrival at another Naval activity. Sulfadiazine prophylaxis was therefore extended to the Out-

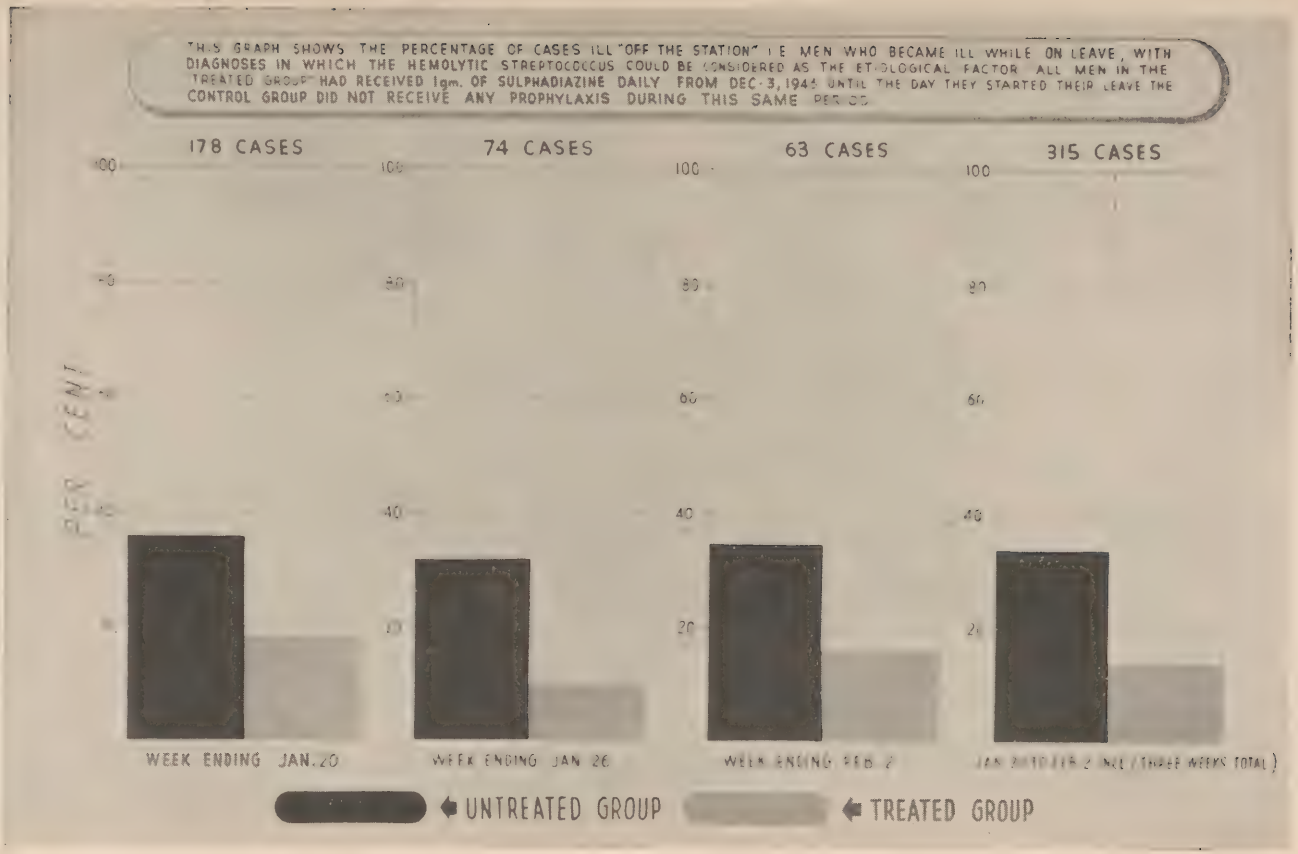

THIS GRAPH SHOWS THE PERCENTAGE OF CASES ILL "OFF THE STATION" I.E. MEN WHO BECAME ILL WHILE ON LEAVE, WITH DIAGNOSES IN WHICH THE HEMOLYTIC STREPTOCOCCUS COULD BE CONSIDERED AS THE ETIOLOGICAL FACTOR. ALL MEN IN THE TREATED GROUP HAD RECEIVED 1gm. OF SULPHADIAZINE DAILY FROM DEC. 3, 1945 UNTIL THE DAY THEY STARTED THEIR LEAVE. THE CONTROL GROUP DID NOT RECEIVE ANY PROPHYLAXIS DURING THIS SAME PERIOD
178 CASES
74 CASES
63 CASES
315 CASES
PER CENT
100
80
60
40
20
WEEK ENDING JAN. 20
WEEK ENDING JAN 26
WEEK ENDING FEB 2
UNTREATED GROUP
TREATED GROUP

CHART 5

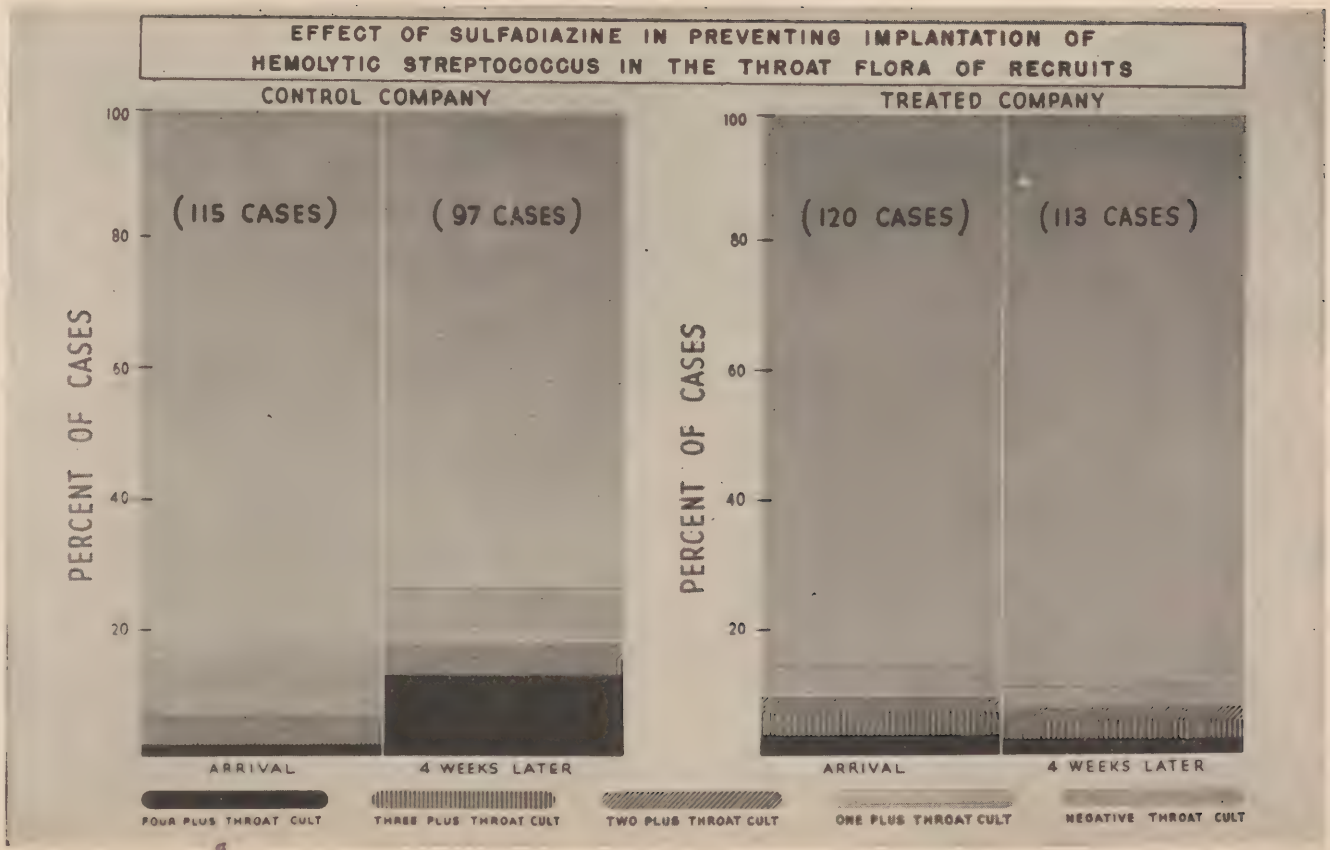

EFFECT OF SULFADIAZINE IN PREVENTING IMPLANTATION OF HEMOLYTIC STREPTOCOCCUS IN THE THROAT FLORA OF RECRUITS
CONTROL COMPANY
TREATED COMPANY
PERCENT OF CASES
100
80
60
40
20
(115 CASES)
(97 CASES)
(120 CASES)
(113 CASES)
ARRIVAL
4 WEEKS LATER
FOUR PLUS THROAT CULT
THREE PLUS THROAT CULT
TWO PLUS THROAT CULT
ONE PLUS THROAT CULT
NEGATIVE THROAT CULT

CHART 6

Going Unit, and several investigations were made to determine whether the sulfadiazine program modified this epidemic process:

1. The illness rate of men on leave who had taken prophylaxis was compared with the rate of illness among men from untreated groups. Favorable effects of sulfadiazine prophylaxis were observed. This is illustrated in chart 5.

2. The incidence of men carrying hemolytic streptococcus in their throat flora at the end of recruit training was determined. It was found to be higher in the untreated companies than in treated companies. This is shown in chart 6.

3. Letters of inquiry were sent to other Naval activities. The response to these requests for information indicated that less infection than had been observed previously occurred among Farragut transfers after all men in the Out-Going Unit had been placed on sulfadiazine prophylaxis.

Evaluation of 0.5 Gm. of Sulfadiazine as a Prophylactic Dose.—The importance of determining the minimal effective daily prophylactic dose of sulfadiazine is obvious. Initial studies in Camps Peterson (E) and Scott (F) showed that 0.5 gm. was effective in controlling streptococcal illness. A comparison was then made between recruits receiving 1 gm. and those receiving 0.5 gm. of sulfadiazine prophylactically. On 6 February the odd-numbered companies in previously untreated camps, Waldron (A) and Ward (B), were given 0.5 gm. of sulfadiazine daily and the even companies were given 1 gm. daily. This was continued for a 6 weeks' period.

Companies were assigned odd or even numbers alternately at the Receiving Unit. A random distribution of such environmental influences as barracking, time in camp, messing, and other factors in the groups was assured. The diagnoses of patients admitted to the dispensaries and hospital were checked and the number of men appearing at sick call with respiratory illness was recorded. Careful physical examinations of as many patients with respiratory illness as possible were made by medical officers of the Epidemiology Unit, and throat cultures taken at this time were examined for hemolytic streptococci. Data on the effectiveness of the two dosages are presented in table 3.

Table 3, comprising the morbidity data obtained from the admission diagnoses in the two groups, shows that the differences in effectiveness of the two dosages are slight. In catarrhal fever, in total respiratory infections, and in total respiratory sick call there is a small but statistically significant difference in favor of 1 gm. of sulfadiazine over 0.5 gm.; however, the incidence of diseases commonly considered to be streptococcal in origin, such as pharyngitis, tonsillitis and scarlet fever, was lowered as effectively by 0.5 gm. as by 1 gm. of sulfadiazine. If all the diseases whose causative agents have been found susceptible to sulfadiazine prophylaxis are grouped together (total of respiratory infections in table 3),

TABLE 3.—*Comparison of effectiveness of 2 chemoprophylactic dosages*

Clinical diagnoses	0.5 gm. (5,331)*		1.0 gm. (5,631)*		Relative effectiveness		
	No. of cases	Rate 1000/week	No. of cases	Rate 1000/week	Best dosage	Diff. in rate	Prob. in 100 due to chance
Scarlet fever	59	1.84	63	1.83	1.0 gm.	0.01	90–95
Tonsillitis	18	0.56	24	0.70	0.5 gm.	0.14	40–50
Pharyngitis	25	0.78	28	0.81	0.5 gm.	0.03	80–90
Sinusitis	5	0.16	8	0.23	0.5 gm.	0.07	30–40
Otitis media	44	1.37	37	1.08	1.0 gm.	0.29	30–35
Other suppurative infections	4	0.12	10	0.29	0.5 gm.	0.17	10–20
Pneumonia—all types	17	0.52	21	0.61	0.5 gm.	0.09	60–70
Catarrhal fever	215	6.73	180	5.23	1.0 gm	1.50	2
Rheumatic fever	19	0.59	18	0.52	1.0 gm.	0.07	70–80
Total	406	12.70	389	11.50	1.0 gm.	1.20	10–20
Respiratory sick call	2,578	80.60	2,586	75.03	1.0 gm.	5.57	2–5

* Average weekly population.

a difference in morbidity rate of only 1.10 per thousand men per week is found in favor of 1 gm. over 0.5 gm. Between 20 and 30 times out of a hundred, such a difference could arise by chance. In a smaller group of patients given more detailed diagnostic examination by the epidemiologic medical officers, no significant difference in the effectiveness of the two drug dosages could be shown. Furthermore, in these patients cultures of the throat showed no significant differences; the percentages of culture negative and positive for hemolytic streptococcus were similar in the two groups.

In summary, 0.5 gm. appears to be approximately as effective as 1 gm. in preventing streptococcal infections. The rate of untoward reactions is lower with the smaller dose. The simplicity of administration and the saving in cost of the drug favor the use of 0.5 gm. daily. It is obvious that in any future prophylactic use of sulfadiazine 0.5 gm. of this drug daily should be tested on a large scale.

Man-Days Saved

The first 3 months of the controlled program saved more than 100,000 man-days of enlisted personnel and concomitantly relieved heavy demands on medical personnel. The extension of sulfadiazine prophylaxis can be expected to create a greater saving.

The direct saving in man-days was estimated on the assumption that the difference in illness between control and treated groups represented the amount of illness prevented. Figures for man-days lost for each type of illness were obtained from the Bureau of Medicine and Surgery. The number of admissions saved was calculated separately for each type of Naval personnel for each disease. This was done by comparing the admission rates in control and treated areas where controlled observations were made or, in the case of the Out-Going Unit and of the Ship's Company, by comparing the admission rates before and after the administration of sulfadiazine. Man-days saved were then the product of admissions prevented in each disease and the average number of sick days for each type of illness. Figures were adjusted to the basis of 1,000 men taking prophylaxis for 1 week. From this, figures on man-days saved in actual administration could be simply calculated, because it was known how many men had been taking prophylaxis and for how long a time.

The effectiveness of sulfadiazine prophylaxis in saving man-days is determined by several factors:

1. The greater the amount of respiratory disease occurring in a group, the greater will be the saving in man-days as a result of sulfadiazine prophylaxis. For example: More illness can be prevented among recruits with a high rate of infections than in seasoned men of Ship's Company with a low rate of infections.

2. The greater the bacteriostatic effect of the drug, the greater the savings will be as a result of prophylaxis. For example: Sulfadiazine is more effective in preventing scarlet fever or meningitis than pneumonia.

3. The more time required for recovery from a particular disease, the more man-days will be saved. For example: The man-days lost for one admission with rheumatic fever is equivalent to about 16 admissions for acute tonsillitis.

4. The greater the number of man-days of sulfadiazine prophylaxis, the larger will be the number of man-days saved.

The relation of some of these factors to the accumulated man-days saved is shown in tables 4 and 5. It is seen in these tables that the saving in man-days at Farragut occurred among recruits and that this was due especially to the prevention of scarlet fever and rheumatic fever. Such a preventive measure also carries with it a tremendous saving in salaries and pensions.

TABLE 4.—*Saving in man-days by prevention of respiratory illnesses with sulfadiazine prophylaxis, December 1943 to April 1944*

Groups of personnel	Saving per 1000/week	Man-weeks of prophylaxis	Man-days saved by groups receiving prophylaxis
Recruits	343	248,879	85,372
Special Assignment	248	41,905	10,391
Service Schools	56	47,199	2,643
Out-Going Unit	32	33,787	1,082
Ship's Company	33	17,798	587
Total	*315	389,568	100,075

*Weighted.

TABLE 5.— *Saving in man-days per 1000 of recruits for 10 important respiratory diseases*

Diseases	Regular recruits	Limited duty recruits
Percent of total population	49.1	12.3
Scarlet fever	148.1	29.6
Rheumatic fever	94.5	62.9
Catarrhal fever	41 3	78.1
Tonsillitis	14.1	15.7
Otitis media	15.3	13.4
Bronchitis, laryngitis, etc.	9.2	2.8
(All types) Pneumonia	6.3	32.4
Pharyngitis	6.3	1.6
Sinusitis	5.8	4.6
Meningococcus meningitis	2.4	7.1

Effect of Sulfadiazine Prophylaxis on Prevalence of Hemolytic Streptococcus in Throat Flora.—It is frequently difficult to make an etiologic diagnosis of a respiratory disease on clinical examination. This difficulty is partly overcome by an accurate appraisal of the respiratory pathogens present in the throat flora. We have made careful cultural studies of the throat flora of patients with respiratory infections, primarily as an aid to diagnosis but also to determine the effectiveness of sulfadiazine prophylaxis on the activity of hemolytic streptococcus among Naval personnel.

It is well recognized that persons with streptococcal respiratory disease have a higher proportion of hemolytic streptococcus in their throat flora than those who carry this organism coincidentally, either in the course of a non-streptococcal disease or during good health. We have therefore recorded the incidence of positive throat cultures in the various groups of men and also have determined the proportion of hemolytic streptococci in positive cultures. For convenience we have used the following scale: Predominant is called 4 plus; heavy growth, 3 plus; moderate number, 2 plus; few hemolytic streptococci, 1 plus. Comparisons were made between the throat culture findings in the groups receiving prophylaxis and in the untreated controls.

Initial results showed that (1) the absolute number of patients with throat cultures containing hemolytic streptococci was less in the treated groups; (2) the proportion of all respiratory diseases with positive cultures was less in the treated groups; (3) cultures with a heavy growth of hemolytic streptococci, 3 plus or 4 plus cultures, were strikingly less common in the treated groups. Further studies were then made to determine the influence of sulfadiazine prophylaxis on streptococcal activity.

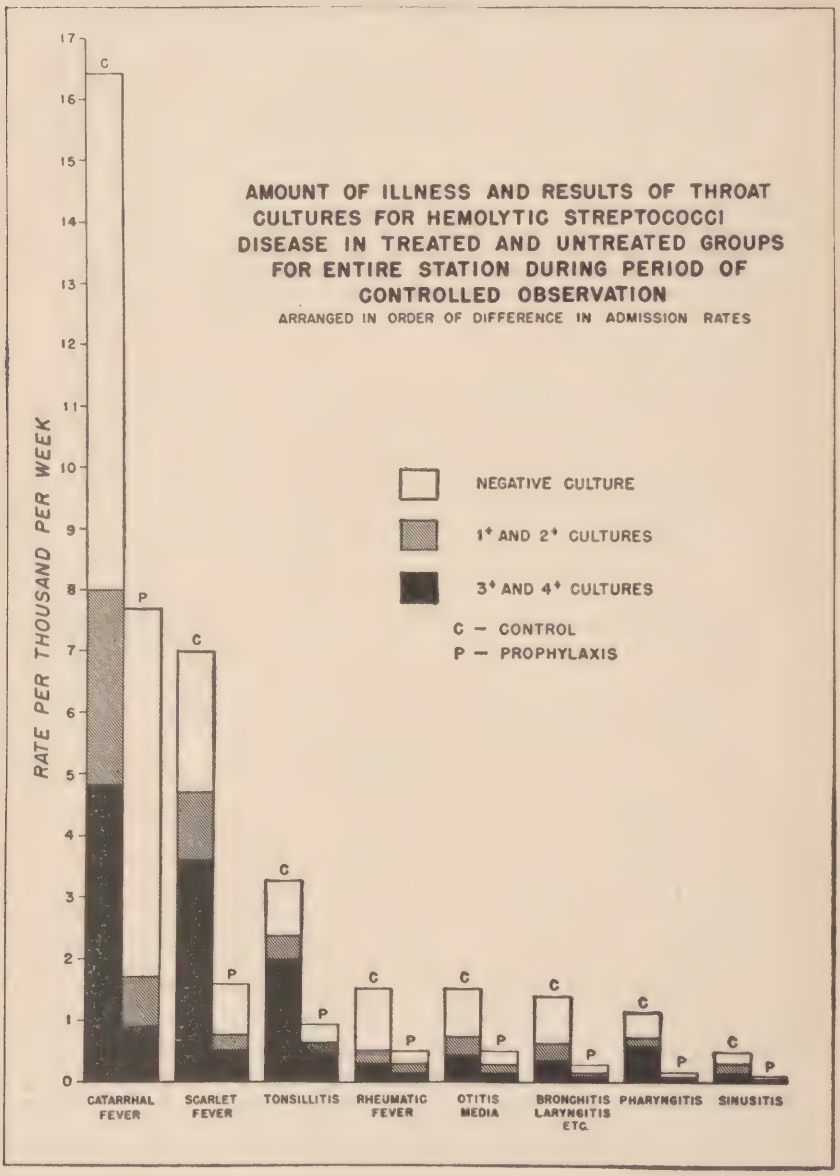
TABLE 6.—*Relation of the presence and proportion of hemolytic streptococcus to sulfadiazine prophylaxis in the throat flora of patients with respiratory diseases*

Throat culture findings	Regular prophylaxis		Irregular prophylaxis		No prophylaxis	
	Number	Percent	Number	Percent	Number	Percent
Negative	261	76.1	90	66.7	226	49.8
One and Two Plus	40	11.7	18	13.3	89	19.6
Three and Four Plus	42	12.2	27	20.0	139	30.6
Total	343	100.0	135	100.0	454	100.0

Men from whom cultures were to be taken were divided into three groups: (1) those who took prophylaxis regularly; (2) those who took prophylaxis irregularly, and (2) those who took no prophylaxis. Studies of throat cultures in these three groups showed that the more regularly

prophylaxis was taken, the more negative cultures there were and the fewer strongly positive cultures were obtained. These data are presented in table 6. It was also found that in patients with the same admission diagnosis, the absolute and relative number of strongly positive cultures was less in the treated than in the untreated group. This was particularly striking in patients with the diagnosis of catarrhal fever (chart 7). In our opinion, there was either more streptococcal disease in the control group or less in the group receiving prophylaxis than is actually

CHART 7



indicated by morbidity rates of frank or presumptive streptococcal disease.

Serologic Types of Hemolytic Streptococci Prevalent at Farragut.—The outstanding clinical characteristics of streptococcal activity at Farragut were: (1) the high incidence of scarlet fever; (2) the high incidence

TABLE 7.—*Incidence of different types of hemolytic streptococci recovered from throat flora of patients with respiratory tract infections at Farragut, January through March 1944*

Group A	Number	Percent
Type 1	60	14 80
2	0	0.00
3	21	5.20
4	1	0.25
5	3	0.74
6	5	1.23
8	1	0.25
9	2	0.49
11	0	0.00
12	3	0.74
14	3	0.74
17	156	38.60
18	6	1.48
19	89	22.00
24	8	1.98
26	0	0.00
28	2	0.49
29	0	0.00
30	1	0.25
32	0	0.00
33	1	0.25
36	7	1.73
39	0	0.00
41	0	0.00
43	0	0.00
44	1	0.25
46	0	0.00
?	34	8.42
Total—Group A	404	91.60
Not Group A*	37	8.40
Total cultures examined	441	

* These specimens include Beta hemolytic streptococcus not of Group A, cultures not Beta hemolytic streptococcus and cultures not suitable for examination on arrival.

and severity of rheumatic attacks following streptococcal infections; (3) the occurrence of a large number of cases of primary streptococcal pneumonia which frequently gave rise to suppurative processes. The rapidity with which these infections were contracted by recruits and the severity of the clinical characteristics indicated that the Farragut strains of hemolytic streptococcus were both highly communicable and unusually virulent. It was, therefore, of interest to determine whether one, several, or many strains were operative at this station. Serologic identification of the causative agents proved helpful in determining this point.

TABLE 8.—*Relative frequency with which prevalent group A types of hemolytic streptococci were associated with respiratory infections at Farragut*

Diagnoses	Serologic type—Group A—hemolytic streptococcus										Total cultures examined
	17		19		1		3		All other known		
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	
Scarlet fever	78	48.4	45	27.9	9	5.6	16	9.9	13	8.1	161
Tonsillitis	16	20.3	19	24.1	18	22.8	5	6.3	21	26.6	79
Pharyngitis	16	41.0	5	12.8	5	12.8	4	10.3	9	23.1	39
Empyema	7	77.8	0	0.0	2	22.2	0	0.0	0	0.0	9
Otitis media, sinusitis peritonsillar abscess, etc.	19	36.9	15	28.4	7	13.2	1	1.9	11	20.8	53
Rheumatic fever	9	60.0	3	20.0	2	13.3	0	0.0	1	0.7	15
Catarrhal fever	38	31.1	37	30.3	16	13.2	7	5.7	24	19.7	122
Virus respiratory disease (measles, mumps, etc.)	8	40.0	2	10.0	3	15.0	1	5.0	6	30.0	20
"Normals"	3	15.8	4	21.1	9	47.4	1	5.3	2	10.5	19

Altogether 441 cultures from patients with respiratory diseases were shipped during the winter months to the Bethesda laboratory for typing. The results are presented in table 7. It is seen in this table that many serologic types were recovered from different respiratory diseases, but that type 17 was the most common respiratory pathogen in the throats of these patients. Table 8 shows further that type 17, in relation to all other serologic types, appeared with frequency in scarlet fever, rheumatic fever, and empyema. Types 3 and 19 also caused scarlet fever frequently and type 1 gave rise to empyema. It appeared, nevertheless, that the excessively high morbidity rates for scarlet fever, rheumatic fever, and streptococcal empyema at Farragut were associated with the activity of group A, type 17, hemolytic streptococcus.

Untoward Sulfonamide Reactions

Difficulties anticipated at the onset of this program included: (1) high incidence of sulfadiazine sensitization phenomena; (2) severe drug reactions terminating fatally; (3) sensitizing a large number of personnel to sulfonamide. Some of these anticipated untoward effects materialized.

Mild Sensitization Phenomena.—During the first 4 months of this sulfadiazine program, Naval personnel at this training center had approximately 350,000 man-exposure weeks to sulfadiazine prophylaxis. It is estimated that approximately 80,000 men have already received sulfadiazine prophylaxis. Recruits in the Service Schools have received prophylaxis for as long as 16 weeks. The average period in which each man received sulfadiazine was about 4½ weeks.

Mild evanescent dermal reactions, exhibited as a scarlatiniform or morbilliform eruption, were relatively common. In the examination of 16,303 recruits, 0.47 percent of those taking 0.5 gm. daily and 0.75 percent of those taking 1 gm. daily were found to have rashes on the day of examination. The clinical characteristics of all types of reactions are reported by other Naval Epidemiology Units in the following pages. A brief account of the severe reactions is given in this report.

Severe Drug Reactions.—Severe reactions were rare; three types were observed: (1) exfoliative dermatitis; (2) bullous skin lesions; (3) granulocytopenia. During the 4-month period covered by this report there were 39 severe reactions. These included untoward effects from both therapeutic and prophylactic doses of sulfadiazine. The association of three types of reactions with chemoprophylaxis and chemotherapy is shown in table 9.

There were six fatalities from sulfonamides during this program; all resulted from granulocytopenia. Two of these occurred among men on leave, and four in Farragut Naval Hospital. Of the four in Farragut, one man had received no prophylaxis; the other had aplastic anemia. The one who had received no prophylaxis died following sulfonamide

TABLE 9.—*Association of severe sulfonamide reactions with prophylaxis or therapy*

Disease	Total number	Number from prophylaxis alone	Number from therapy alone	Number from both therapy and prophylaxis
Exfoliative dermatitis	1	1	0	0
Bullous skin and mucous membrane lesions	22	8	0	14
Granulocytopenia	16	3	2	11

therapy. Two of the four had had sulfadiazine prophylaxis and had been given sulfadiazine therapy. One had received prophylaxis and a transfusion with blood containing sulfadiazine. The results indicate that therapeutic doses of sulfonamide aggravated a severe disease process initiated by prophylaxis. They also indicate that if the therapeutic use of sulfonamides is foregone among personnel receiving prophylaxis until the diagnosis is established, fatalities can be prevented.

Observations on the Danger of Sensitizing Naval Personnel.—We have observed that relatively few who have contracted infections while receiving prophylactic doses of sulfadiazine are unable to take therapeutic doses of the drug. For example, 252 of the patients with pneumococcus pneumonia who had on previous occasions received sulfadiazine prophylaxis were treated exclusively and effectively by sulfadiazine in most instances. Furthermore, many who showed an initial dermal reaction to the sulfadiazine were subsequently replaced on the program without ill effects. All these men were observed closely when sulfadiazine prophylaxis was resumed after an interval of 2 weeks.

Sulfadiazine was given for as long as 2 months in the Out-Going Unit to all recruits who returned from their 2 weeks' leave. These recruits had received the drug during their "boot" training, had discontinued it for 2 weeks, and then resumed prophylaxis. This incidence of drug reactions was not increased.

In summary, a small percentage exhibited sensitivity to prophylactic or therapeutic doses of sulfadiazine. The prophylactic program did not appear to sensitize large numbers of men.

Observations Regarding Possible Development of Sulfonamide Resistance by Respiratory Pathogens

With the extension of sulfadiazine prophylaxis to the entire station, attention was directed to determining whether the prevalent strains of hemolytic streptococcus might develop resistance to sulfadiazine. If drug resistance did develop, it could be expected to manifest itself in one or more of the following ways:

1. During the continuation of the prophylactic program the morbidity rate of streptococcal diseases would increase as the resistant organisms gained in prevalence.

2. Certain types of group A organisms might develop more resistance than others and would accordingly appear with increasing frequency in throat cultures of patients with upper respiratory tract diseases.

3. Bacterial infections, previously amenable to sulfonamide therapy, would become increasingly more difficult to treat with this chemotherapeutic agent.

4. Hemolytic streptococci or other organisms isolated from treated patients would show evidence of sulfonamide resistance by laboratory tests.

Evidence that drug resistance did not develop during this 4-month period is presented in the following paragraphs:

Effect of Continued Sulfadiazine Prophylaxis on Rate of Illness.—In February, Camps Bennion (C) and Hill (D), which had been on the program longest, experienced an increase in the respiratory sick call rate and in total respiratory infections. This rise was associated in Camp Hill (D) with an increase in streptococcal infections (scarlet fever, tonsillitis and pharyngitis) but this was not apparent in Camp Bennion (C). Because the rising morbidity rate at Hill (D) might indicate a decrease in the effectiveness of the program, this possibility was investigated during the first 2 weeks in April. All patients with respiratory illness were seen by the medical officers of the Epidemiology Unit. Throat cultures were taken and sulfadiazine blood level determinations were made for patients believed to have streptococcal disease.

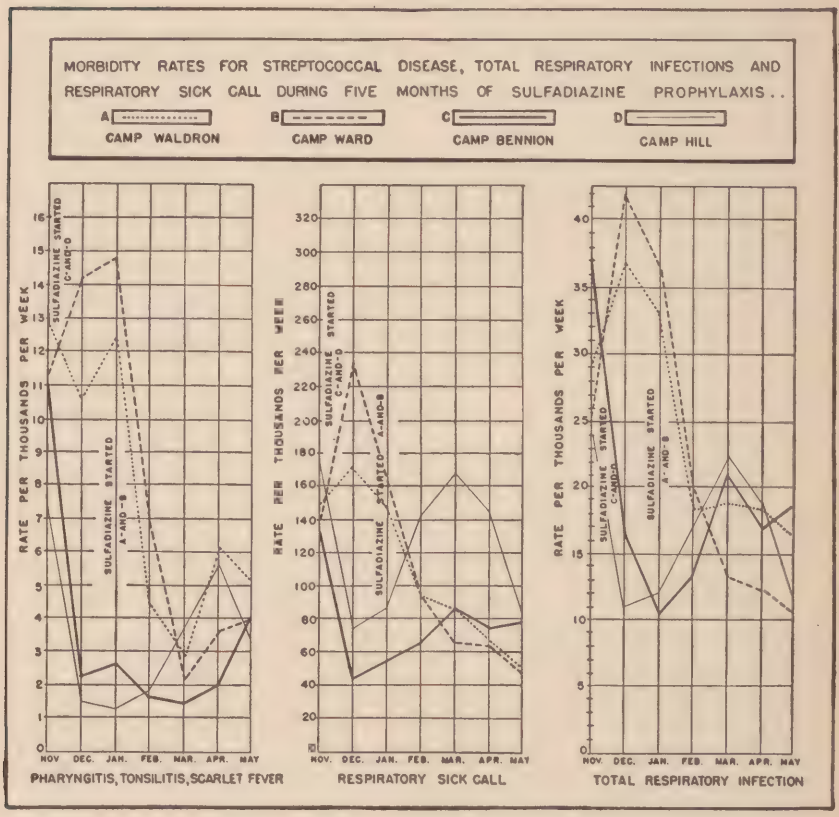
The observations indicated that there was an increase in the streptococcal diseases over the first months of the program. The number of positive cultures, and particularly 3 and 4 plus cultures, was higher in April than in December and January. This is shown in table 10. The mean blood level of 26 patients with positive cultures was 1.38 mg. percent; 6 of these patients had values above 2 mg. percent.

One might expect that the rising rates of upper respiratory tract diseases would be higher in the camps on the drug program for the longest period and less marked in the camps most recently placed on prophylaxis. As the morbidity statistics for April were recorded week by week, it became apparent that the rise in streptococcal morbidity was occurring in all recruit areas and was not related to the time that they had been on prophylaxis. This is shown in chart 8. Further confirmation was obtained by sample throat cultures taken from patients with respiratory diseases in the different areas. Although not strictly comparable, the results indicated that Camp Hill (D) had no higher rate than many other areas and that Camp Bennion (C) had the lowest rate of all recruit groups.

TABLE 10.—*Prevalence of hemolytic streptococci in throat cultures taken from a random sample of respiratory disease in early winter and spring*

Throat culture findings	January and February		April	
	Number	Percent	Number	Percent
Negative	148	81.4	100	50.0
One and two plus	11	6.0	30	15.0
Three and four plus	23	12.6	70	35.0
Total	182	100.0	200	100.0

CHART 8



In summary, a rise in streptococcal disease rate did occur; however, it was independent of the length of time in which the sulfadiazine program had been in effect. We are of the opinion that this rise was a reflection of the general increase in streptococcal infection usually seen in civilian and untreated military populations during March and April. The collected observations showed that there was no relation between prolonged chemoprophylaxis and diminution in effectiveness.

Prevalence of Different Types of Hemolytic Streptococcus During the Program.—If sulfonamide resistance were developing in strains of hemolytic streptococcus, one might anticipate that among those who became infected while receiving prophylaxis there would be an increase in the incidence of certain types because nonresistant types would be less likely to cause illness in these men. The phenomenon of natural selection would be expected to operate, and a resistant strain would become predominant as the program was extended. Furthermore, if a comparison were made between the types recovered from those on prophylaxis and from those in control groups, the more resistant types would appear with greater frequency in the former group. Neither of these possibilities materialized. As is shown in table 11, there was no significant change in the types of streptococci present in respiratory illness in the last 3 months of this program; moreover, there was no essential difference in the distribution of types of hemolytic streptococci recovered from patients with respiratory infections irrespective of whether or not they had received prophylaxis prior to the onset of illness.

In summary, observations made during 3 months of prophylaxis indicated that no strains of hemolytic streptococcus developed resistance to sulfadiazine.

Resistance of Hemolytic Streptococcus to Therapeutic Doses of Sulfadiazine.—Patients with streptococcal infections showed a satisfactory clinical response to sulfonamide therapy throughout this program. Furthermore, a large majority of patients who developed pneumonia despite prophylaxis were treated with sulfadiazine. Approximately 90 percent of these patients responded satisfactorily to sulfadiazine therapy; penicillin was used in the remaining cases. The clinical results of sulfadiazine therapy compared favorably with those of other Naval hospitals. The development of drug fastness was not observed.

Laboratory Investigation of Sulfonamide Resistant Strains of Hemolytic Streptococci.—Strains of hemolytic streptococci obtained in cases of streptococcal infections contracted during prophylaxis were isolated and sent to the National Naval Medical Center, for studies of sulfonamide fastness. Our laboratory also made attempts to show sulfonamide resistance in these organisms. Up to the present time there has been no evidence of drug resistance in group A hemolytic streptococcus at Farragut.

TABLE 11.—*Distribution of types of hemolytic streptococcus in throat flora of patients with respiratory disease during first 4 months of sulfadiazine prophylaxis*

Type	Dec. 24		Jan. 15		Feb. 24		March 15		March 29	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
1	34	21.4	17	9.6	8	8.9	18	11.6	3	2.4
3	7	4.4	11	6.2	3	3.3	8	5.2	12	9.5
4	0	.0	0	.0	4	4.4	0	.0	0	.0
5	2	1.3	1	.6	0	.0	0	.0	1	.8
6	2	1.3	2	1.1	1	1.1	4	2.6	4	3.2
8	1	.6	0	.0	0	.0	0	.0	0	.0
9	2	1.3	0	.0	0	.0	0	.0	1	.8
12	0	.0	3	1.7	0	.0	2	1.3	0	.0
13	0	.0	0	.0	0	.0	1	.6	0	.0
14	0	.0	2	1.1	0	.0	7	4.5	6	4.8
17	56	35.2	67	37.8	32	35.4	49	31.6	26	20.6
18	0	.0	0	.0	2	2.2	2	1.3	0	.0
19	26	16.3	47	26.5	15	16.6	32	20.6	25	19.8
24	1	.6	2	1.1	4	4.4	6	3.9	8	6.3
28	1	.6	1	.6	0	.0	0	.0	0	.0
33	0	.0	1	.6	0	.0	0	.0	0	.0
36	4	2.5	0	.0	2	2.2	4	2.6	2	1.6
41	0	.0	0	.0	0	.0	1	.6	1	.8
41	0	.0	1	.6	0	.0	2	1.3	0	.0
?	10	6.3	11	6.2	12	13.4	14	9.1	33	26.2
Not Group A	11	6.9	11	6.2	7	7.8	4	2.6	.....	3.2
Total	159	.....	177	.....	90	.....	155	.....	126	.....

In summary, no evidence from a clinical, epidemiologic or bacteriologic standpoint was obtained that hemolytic streptococci became resistant to sulfadiazine during 4 months of the prophylactic program.

Comment

Environmental conditions at Farragut Naval Training Center in 1942 and 1943 were favorable to the initiation and perpetuation of epidemics of respiratory tract diseases. Shortly after the opening of this station an excessively high morbidity from streptococcal infections accompanied by high attack rate for rheumatic fever presented a serious problem. It was hoped that activity of hemolytic streptococcus would subside during the summer months of 1943; however, this did not occur. The summer months were dry; daily dust storms, aggravated by the clearing of large areas for construction, were irritating to the respiratory tract; the rate of scarlet fever was maintained at plateau level. An outbreak of influenza (catarrhal fever) occurred in October with the onset of cooler weather; streptococcal activity, already at a high level, increased within a few weeks. By November the morbidity rate from scarlet fever and rheumatic fever was disturbingly high. This was soon followed by the appearance of primary streptococcal pneumonia and empyema. The problem of preventing the dissemination of bacterial respiratory pathogens was complicated by a marked increase in the incidence of measles early in the winter of 1944. All the factors essential for the initiation and perpetuation of a severe streptococcal epidemic, and perhaps even a pandemic, appeared to be operative at this training center. It was urgent to check the dissemination of Streptococcus hemolyticus which had already acquired extensive communicability and to prevent the transmission of these highly pathogenic strains to other environments. Sulfadiazine prophylaxis was selected to attain these objectives, and these objectives were achieved.

Summary

1. A prolonged epidemic of streptococcal diseases, characterized at first by large numbers of cases of scarlet fever and rheumatic fever, and later by the development of cases of primary streptococcal pneumonia occurred at the United States Naval Training Center, Farragut, Idaho, during 1943 and 1944.

2. Sulfadiazine prophylaxis was instituted in December 1943. At first, a controlled study was made; later, all personnel on the station were given chemoprophylaxis, 1 gm. daily.

3. Morbidity rates and bacteriologic studies of treated and untreated groups served as the basis for reaching the following conclusions:

(a) The number of patients reporting to sick call with minor respiratory symptoms but not requiring admission was markedly reduced.

(b) The admission rates for bacterial respiratory tract infections were significantly reduced in those recruits who received prophylactic doses of sulfadiazine.

(c) The fall in the incidence of catarrhal fever, scarlet fever, tonsillitis, pharyngitis, suppurative infections, and rheumatic fever was striking.

(d) Primary streptococcal pneumonia was eliminated by sulfadiazine prophylaxis.

(e) No case of meningococcus meningitis occurred in those taking sulfadiazine prophylaxis.

(f) The incidence of virus infections, such as measles and mumps, was not affected by sulfadiazine prophylaxis.

4. As the portion of the station receiving prophylaxis was increased, the morbidity rate for all respiratory diseases declined.

5. Although the attack rate from pneumonia was less in treated than in control groups, the morbidity rate for pneumococcus pneumonia remained high even after the entire station was placed on a program of sulfadiazine prophylaxis. Clinical and laboratory observations indicate that strains of type 5 pneumococcus prevalent at Farragut were resistant to small concentrations of sulfadiazine.

6. Less illness occurred among recruits on leave from the camps receiving prophylaxis than from camps in which chemoprophylaxis had not been instituted.

7. Administration of the drug to approximately 80,000 men in 3 months saved more than 100,000 man-days on this station. The saving of time was greater among new recruits and is attributed largely to the prevention of scarlet fever and rheumatic fever.

8. Throat cultures obtained from patients with respiratory infections and examined for hemolytic streptococci were more frequently negative and showed less heavy growth in those patients receiving prophylaxis than in the control groups.

9. Type 17 was the most prevalent and perhaps the most pathogenic strain of hemolytic streptococcus at Farragut. Type 19 and type 1 were the next most common.

10. Type 17 was the respiratory pathogen most frequently associated with the development of scarlet fever, rheumatic fever, and streptococcal empyema.

11. In preventing most streptococcal infections, 0.5 gm. of sulfadiazine was approximately as effective as 1 gm.

12. The incidence of dermal reactions was 0.75 percent on 1 gm. dosage, and 0.47 percent on 0.5 gm. dosage.

13. The 3 types of severe sulfadiazine reactions encountered were: (a) exfoliative dermatitis; (b) bullous skin and mucous membrane lesions; (c) granulocytopenia. These reactions were aggravated by the administration of therapeutic doses of the sulfadiazine to men who had received prophylaxis.

14. Six deaths occurred; all were associated with granulocytopenia. With possibly one exception, all are ascribed to therapeutic doses of sulfadiazine.

15. No evidence was obtained from this large number receiving sulfadiazine that prophylaxis sensitizes, or that it militates against the therapeutic application of sulfonamides.

16. There was no evidence that hemolytic streptococcus became sulfonamide-fast during this prophylactic program.[1]

17. Mass sulfadiazine prophylaxis is an effective method for controlling bacterial respiratory tract infections.

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[1] During the summer months (since this report went to press) clinical and bacteriologic findings have indicated that strains of Types 19 and 17 recovered at this naval activity are resistant to prophylactic doses of sulfadiazine.

Report 3

A Study of the Sulfadiazine Streptococcus Prophylaxis Program at the Great Lakes Training Center

*From the Epidemiology Unit**

The high incidence of respiratory diseases among personnel of military installations led to the study of prophylactic use of sulfadiazine in reducing the respiratory diseases of proved streptococcal origin and other respiratory diseases. This study was conducted at the United States Naval Training Center, Great Lakes, Illinois, during the period extending from 1 December 1943 to 15 April 1944.

General Description of Naval Station

Great Lakes Naval Training Center is in effect a series of self-sustaining camps, each having its own dispensary and sickbay, mess hall, galley, drill hall, drill field, and recreation facilities. The camps are distributed as follows:

1. Twelve camps are used for training new recruits: six are in the Green Bay area, three in the Downey area, and three are entirely for Negro training

2. Three camps are used for the Service School, Out-Going Unit, and Marine barracks. For administrative purposes, men in the Service School are divided into Group I, Group II, and Group III. This grouping was used in selecting the men who were to be treated, and to be held as controls.

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Technical Assistants: A. W. N. King, PhM1c, USNR; Glen E. Finley, PhM1c, USNR; Richard C. Hartsfield, PhM1c, USNR; Ramona E. Nieberding, PhM1c, USNR; Jo A. Robar, PhM1c, USNR; Martin G. Austin, PhM2c, USNR; Carlyle D. Hummel, PhM2c, USNR; Dorothea D. McCreedy, PhM2c, USNR; Thomas C. Kessler, PhM2c, USNR; Rosalie M. Erspamer, PhM2c, USNR.

3. One camp is used as a reception center. The recruits are examined here and then assigned to recruit camps.

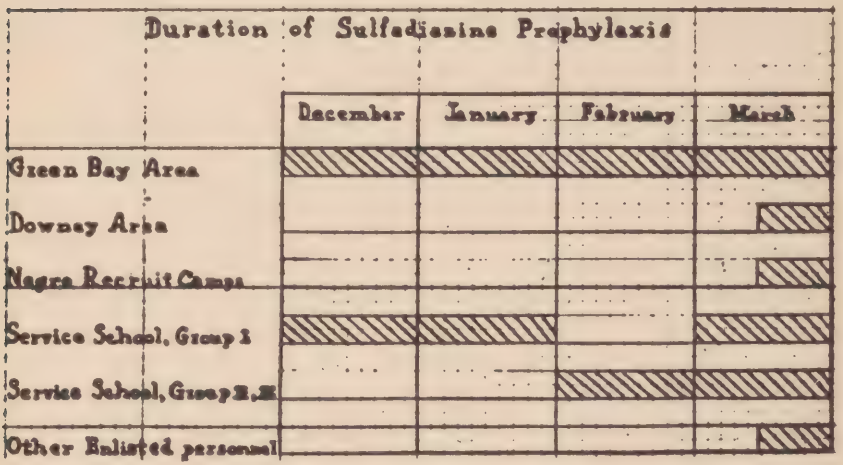
4. One camp (Camp McIntire or McIntire Dispensary) is essentially the hospital, taking care of those patients whose condition is too serious to be cared for in the outlying camp dispensaries. Most patients with scarlet fever, mumps, and German measles are sent to McIntire. All other patients with contagious diseases are sent to the nearby U. S. Naval Hospital, which comprises a separate command from that of the Training Center.

5. All these various activities are closely knit together by the "Main Side" area which houses the administrative offices.

Method

The task of carrying out this study was given to the Epidemiologic Unit, consisting of five medical officers, two H-V(S) officers, and nine hospital corpsmen. Chart 9 shows the plan for distribution of sulfadiazine prophylaxis among the several participants.

CHART 9



Beginning 1 December 1943, the recruits in the Green Bay area and the men in Service School, Group I, were given 1 gm. of sulfadiazine daily, and the recruits from Downey area and the men in Service School, Groups II and III, were held as controls. The Green Bay area was selected for the treated group because this area had a previous incidence of respiratory diseases consistently higher than the Downey area; Service School, Group I, was chosen arbitrarily. This plan among the recruits (Downey and Green Bay Areas) was not changed until 13 March 1944, when both areas were placed on a program of sulfadiazine prophylaxis. The Service School plant (Groups I, II, and III) was not changed until 1 February 1944, when Groups II and III were given sulfadiazine and

Group I was held as control. On 1 March 1944, all the Service School (Groups I, II, and III) were given sulfadiazine.

On 13 March 1944, the program was extended, so that all the enlisted personnel attached to Great Lakes Naval Training Center received sulfadiazine prophylactically.

Insofar as possible, the men ingested the drug under direct supervision of company commanders, Service School instructors, and departmental representatives. The two tablets (0.5 gm. each) were taken together, at a regular time during the day compatible with the daily routine.

A throat culture for beta hemolytic streptococci and a blood sulfadiazine level were taken of all patients admitted for respiratory disease. Diagnoses of rheumatic fever, pneumonia, meningitis, and scarlet fever made on admission were confirmed by personal follow-up. Diagnoses of all other respiratory diseases were accepted.

All men with a definite or suggested sulfonamide reaction were withdrawn from the program. Insofar as possible a medical officer of the epidemiology unit personally observed all eruptions and retested a large percentage. A throat culture and blood sulfadiazine level were taken of all reactors.

All the beta hemolytic streptococci isolated from the sulfadiazine-treated and control patients were subcultured and sent to the laboratory at the National Naval Medical Center for grouping and typing.

A sampling of leukocyte counts and urinalyses was taken to determine the prevalence of untoward effects of prophylactic sulfadiazine on the hematopoietic and urinary systems.

The weekly and monthly incidences of the various respiratory diseases among the treated and untreated groups were calculated and graphed. An epidemiologic study of the streptococcus types was done. An evaluation of the frequency, severity, and modifying factors of sulfadiazine skin manifestations was made.

The following diseases are referred to by the term "upper respiratory infections": scarlet fever; tonsillitis, acute; pharyngitis, acute; catarrhal fever, acute; laryngitis, acute; bronchitis, acute; tracheitis, acute; rhinitis, acute; Vincent's infection; sinusitis, acute; otitis media, acute; mastoiditis, acute; tracheobronchitis.

When "all respiratory infections" are mentioned, the following are included in addition to the listed diseases: primary atypical pneumonia; bronchopneumonia; lobar pneumonia; cerebrospinal fever (meningococcus).

Effect of Prophylactic Sulfadiazine on Respiratory Diseases

Daily Respiratory Complaints at Sick Calls.—Charts 10 and 11 show that immediately following the institution of sulfadiazine prophylaxis in the recruit camps and Service School the respiratory symptoms in the

treated groups fell precipitously; whereas the control groups varied according to seasonal incidence. The rates in the Service School before the program was begun unfortunately cannot be shown because the groupings of the men reporting at sick call were not recorded prior to the institution of the program. It is not clear why the rates in the treated recruit camps gradually increase and approach the rates of the untreated camps; however, the rates in the treated recruit camps never reached the levels obtained before the program was begun. It should be pointed out that the increase in the rates of respiratory symptoms among the treated groups was not reflected in the admissions for respiratory disease. The precipitous fall in the rates of the controls in the recruit camps as shown in chart 10 was coincident with expansion of the program to include all enlisted personnel.

Chart 11 shows the constant level of the respiratory symptoms among the treated men (Group I) of Service School as contrasted with the findings shown in chart 10. As soon as prophylaxis was discontinued the respiratory complaints increased.

Total Admissions for Respiratory Diseases to Dispensaries and Hospital.—Charts 12 and 13 show the striking and sustained difference between the rates of admissions for respiratory disease in the treated and control groups in both the recruit camps and the Service School.

It is seen from chart 13 that the admission rates in Group I did not greatly increase during the month of February even though prophylaxis was discontinued during that month; possibly this resulted from reduction of bacterial flora during the previous period of sulfadiazine prophylaxis.

Effect of Prophylactic Sulfadiazine on Diseases of Streptococcal Origin

Charts 14 and 15 show the persistent effect of prophylactic sulfadiazine in reducing the incidence of scarlet fever, tonsillitis, and pharyngitis among the treated men in the recruit camps and the Service School.

Effect of Prophylactic Sulfadiazine on Incidence of Catarrhal Fever

Chart 16 shows a precipitous decrease in the incidence of catarrhal fever among the treated recruits. This behavior is not compatible with the accepted virus etiology of the group of upper respiratory diseases called "catarrhal fever" in Navy nomenclature. Several explanations might be offered, prominent among which is the one that many "catarrhal fevers" are in reality beta hemolytic streptococcus infections with constitutional rather than local symptoms predominating. The evidence for this conception is the striking similarity between the figures depicting the behavior of streptococcus infections and catarrhal fever in the recruit camps. Further, it has been observed that 2.4 percent of 781 men with catarrhal fever taking prophylactic sulfadiazine had throat cultures posi-

CHART 10

All Complaints for Respiratory Diseases
Among Recruits in Treated and Control Camps
Rates per 1000 per Week
Treated Group
Control Group
Rate per 1000 per Week
November
December
January
February
March

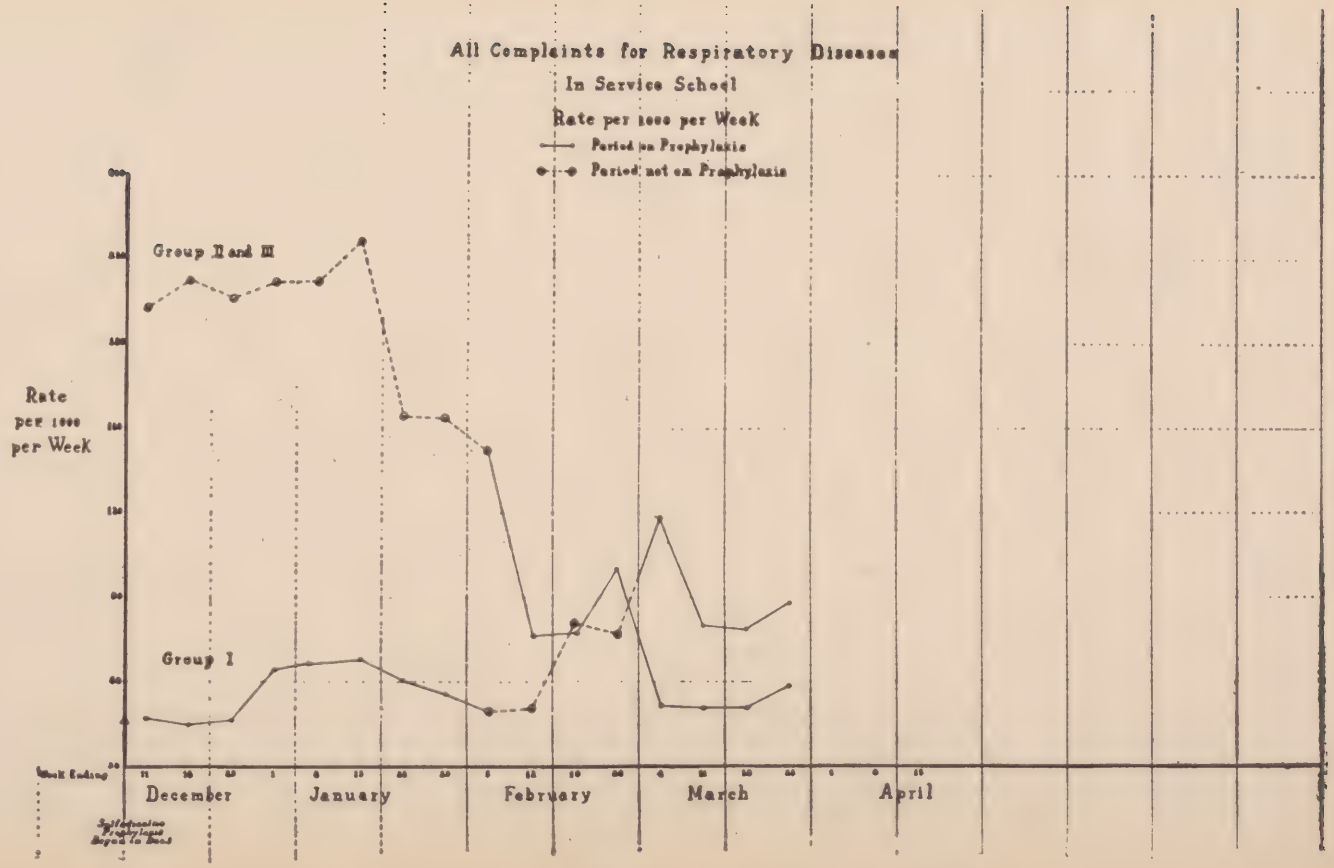

All Complaints for Respiratory Diseases
In Service School
Rate per 1000 per Week
Period on Prophylaxis
Period not on Prophylaxis
Group II and III
Group I
Rate per 1000 per Week
December
January
February
March
April

CHART II

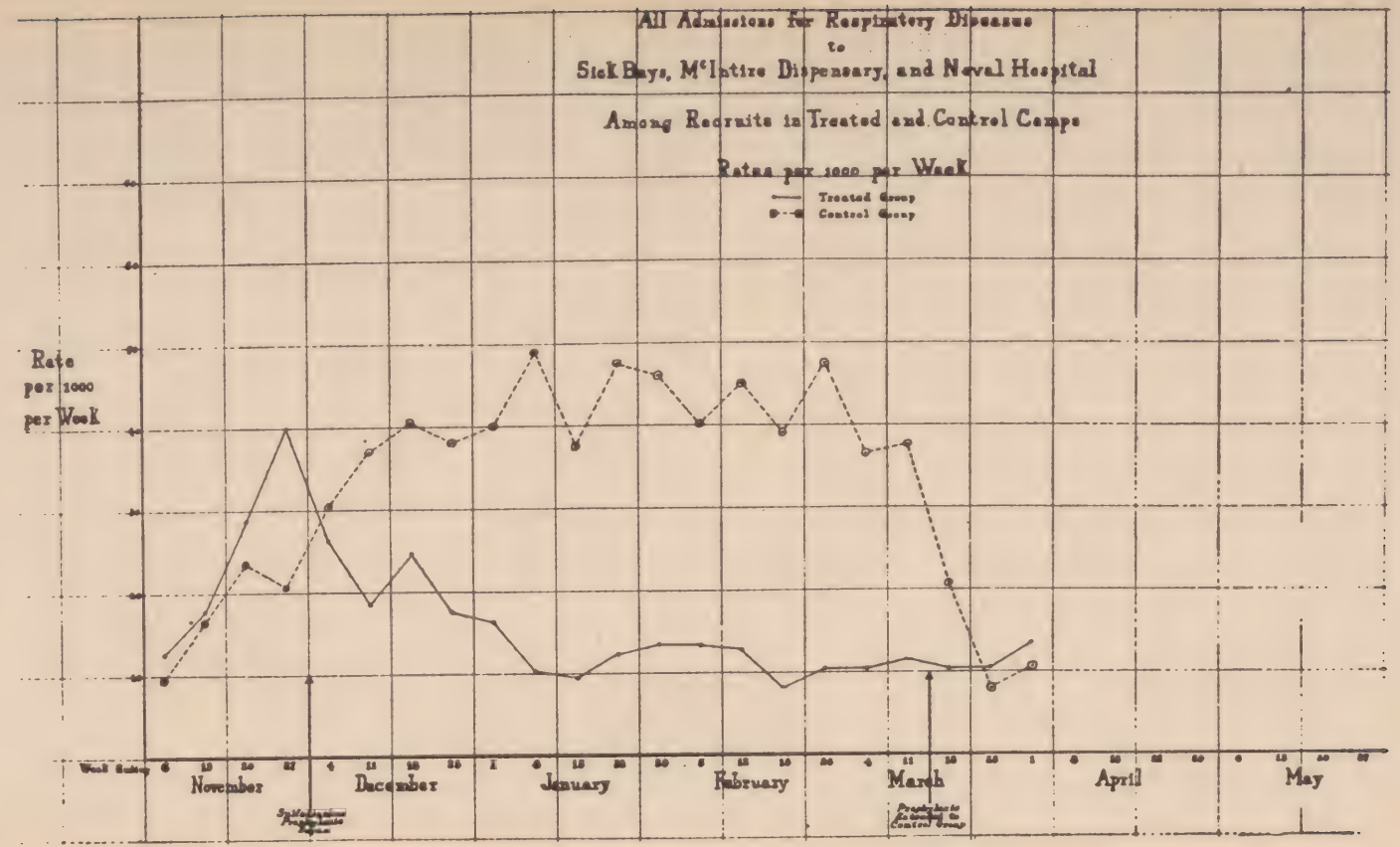

All Admissions for Respiratory Diseases
to
Sick Bays, McIntire Dispensary, and Naval Hospital
Among Recruits in Treated and Control Camps
Rates per 1000 per Week
Treated Group
Control Group
Rate per 1000 per Week
November
December
January
February
March
April
May

CHART 12

CHART 13

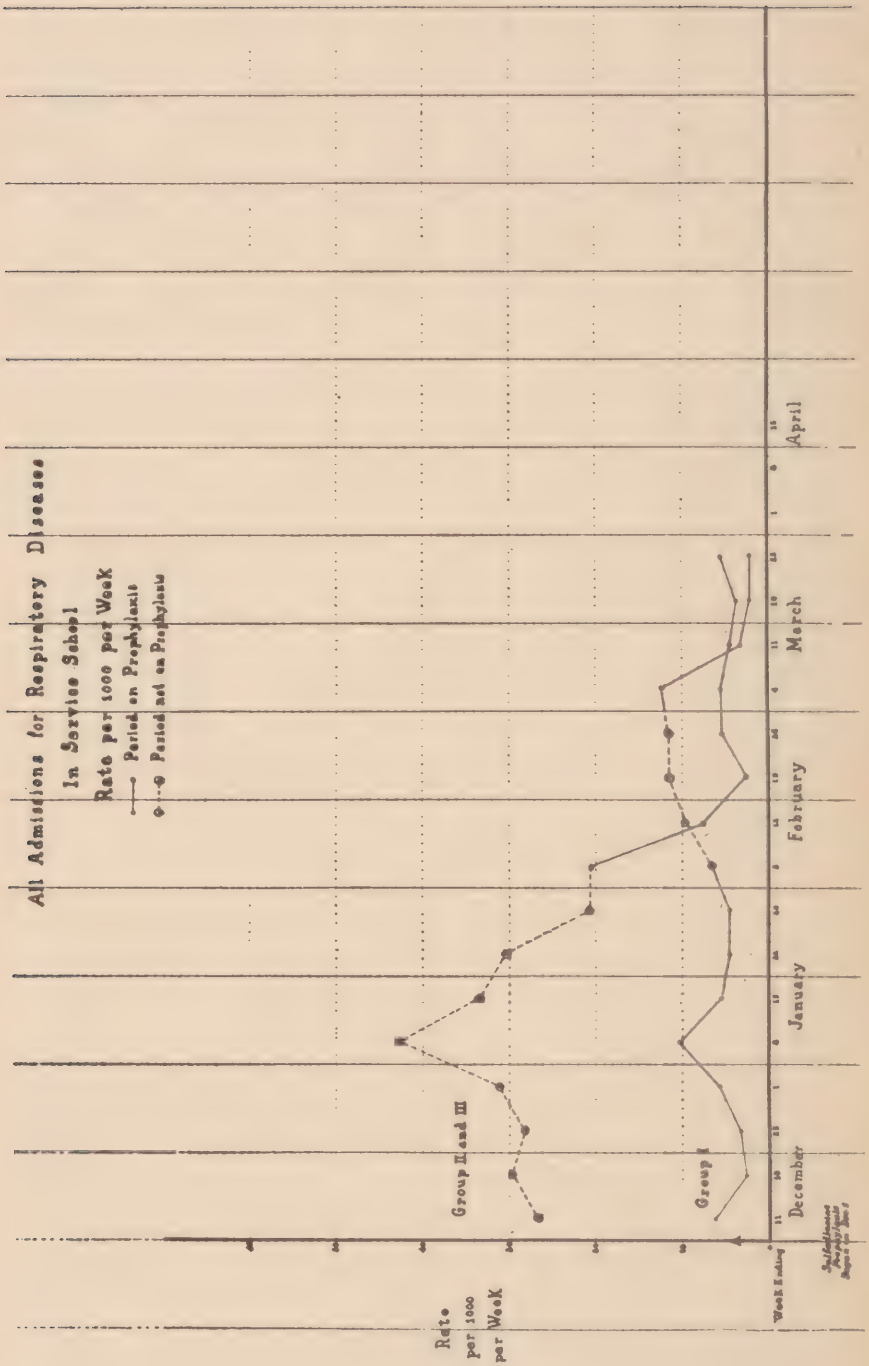

All Admissions for Respiratory Diseases
In Service School
Rate per 1000 per Week
Period on Prophylaxis
Period not on Prophylaxis
Rate per 1000 per Week
Group II and III
Group I
December
January
February
March
April

CHART 14

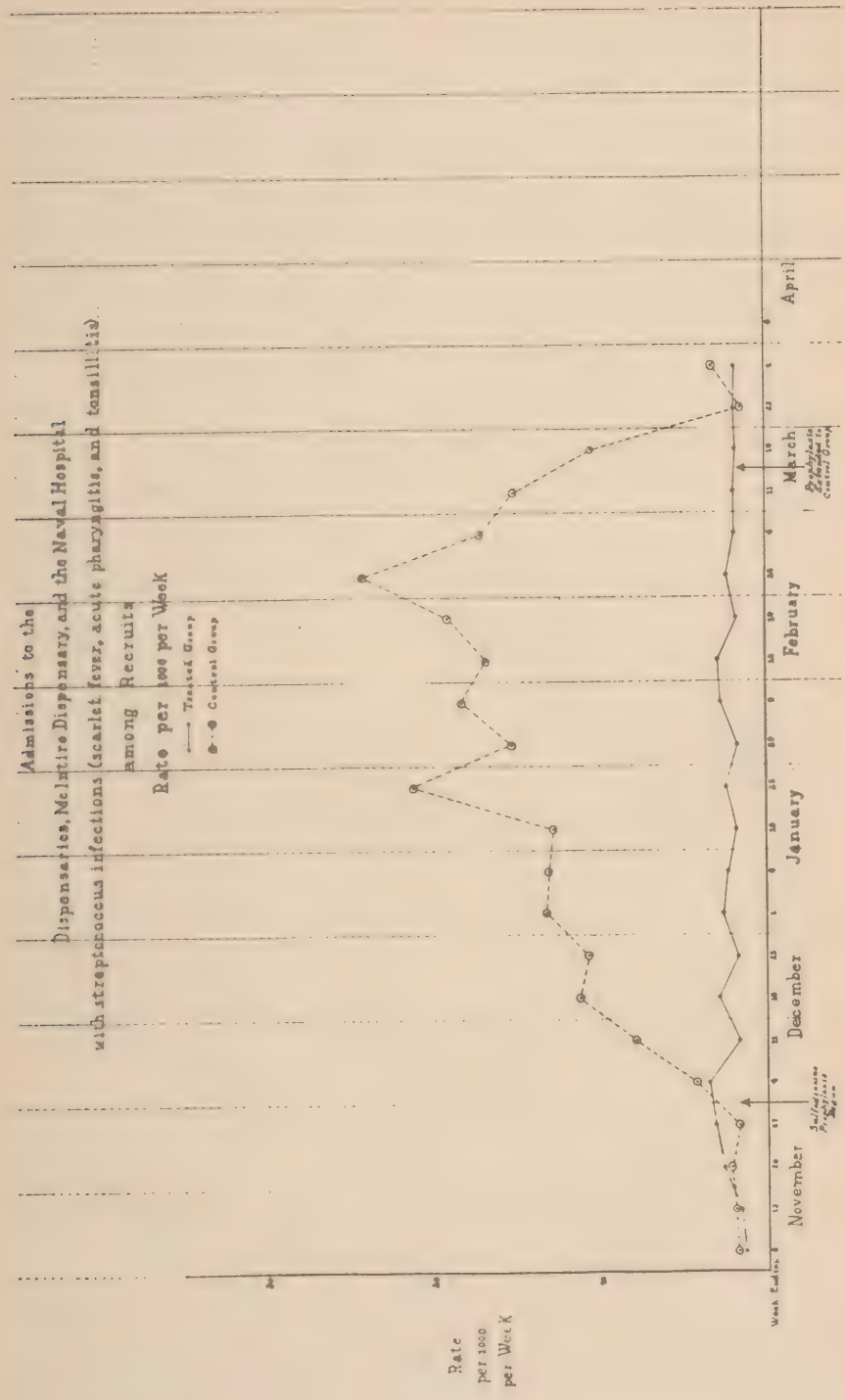

Admissions to the
Dispensaries, Melxtire Dispensary, and the Naval Hospital
with streptococcus infections (scarlet fever, acute pharyngitis, and tonsillitis)
among Recruits
Rate per 1000 per Week
Tested Group
Control Group
Rate per 1000 per Week
November
December
January
February
March
April

CHART 15

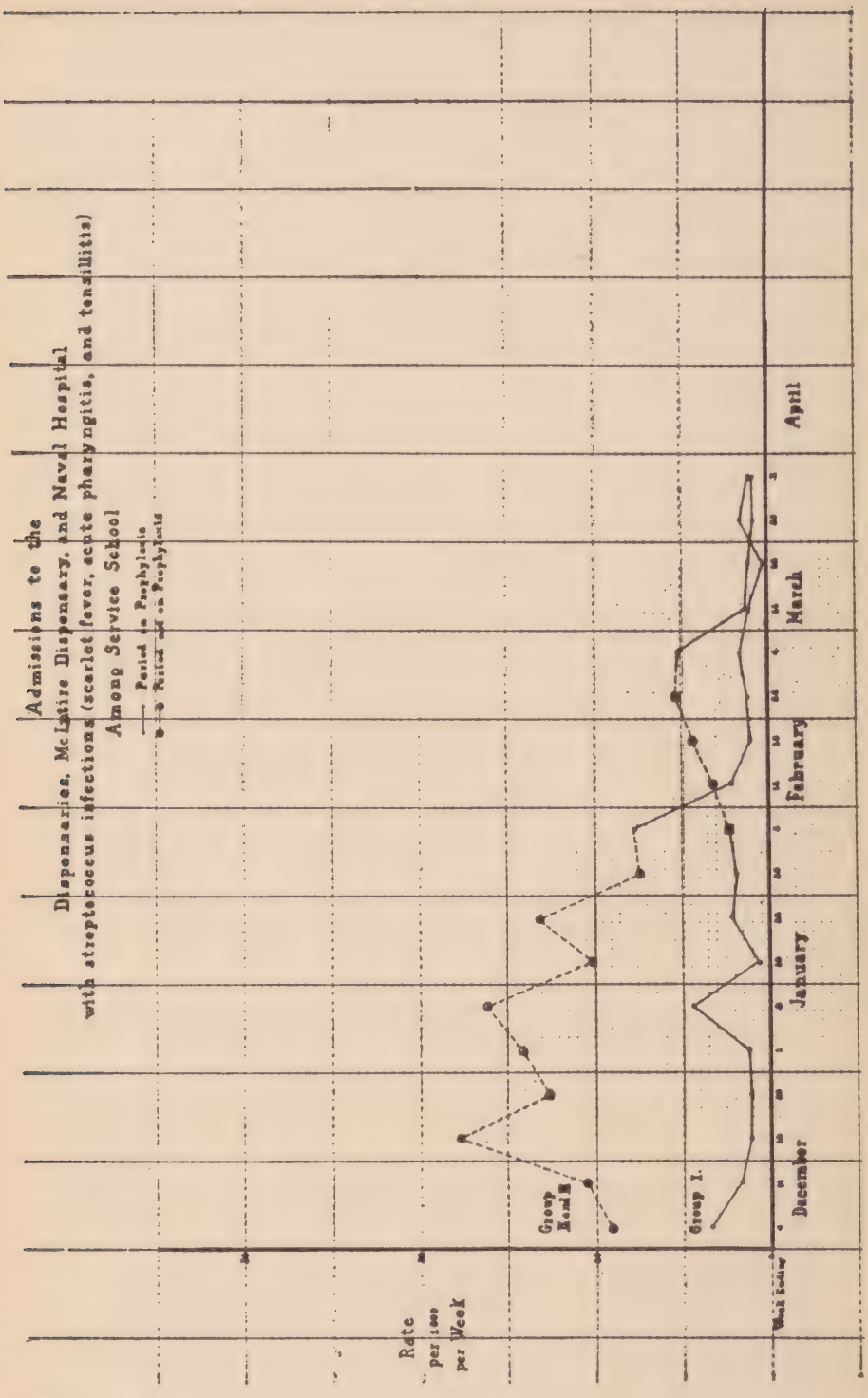
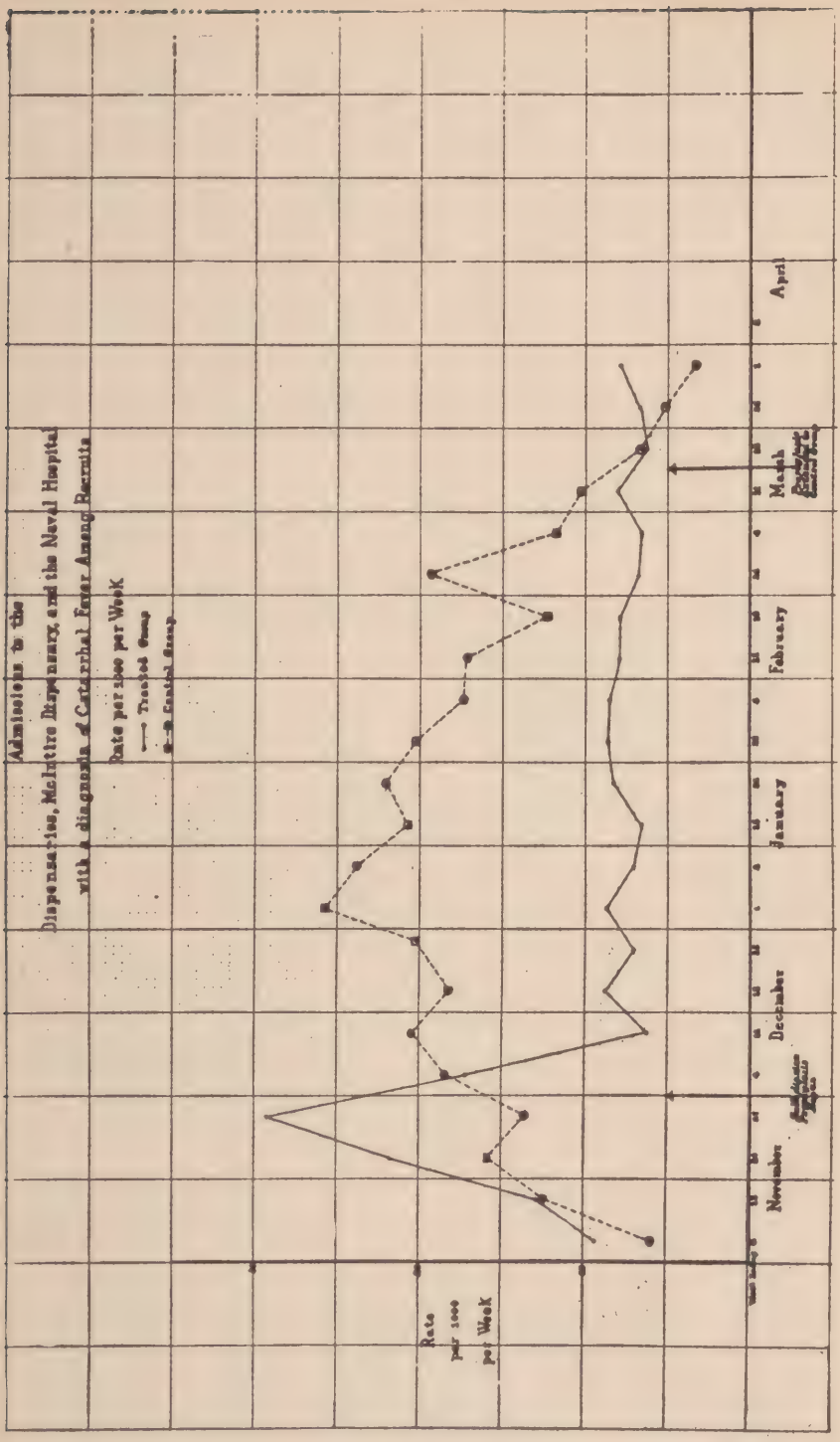

Admissions to the
Dispensaries, McLaire Dispensary, and Naval Hospital
with streptococcus infections (scarlet fever, acute pharyngitis, and tonsillitis)
Among Service School
Period of Prophylaxis
Rate per 1000 per Week
Group I.
Group II.
December
January
February
March
April

CHART 16


Admissions to the
Dispensaries, Melville Hospital, and the Naval Hospital
with a diagnosis of Catarrhal Fever Among Recruits
Rate per 100 per Week
Tracked Group
Control Group
Rate per 100 per Week
November
December
January
February
March
April

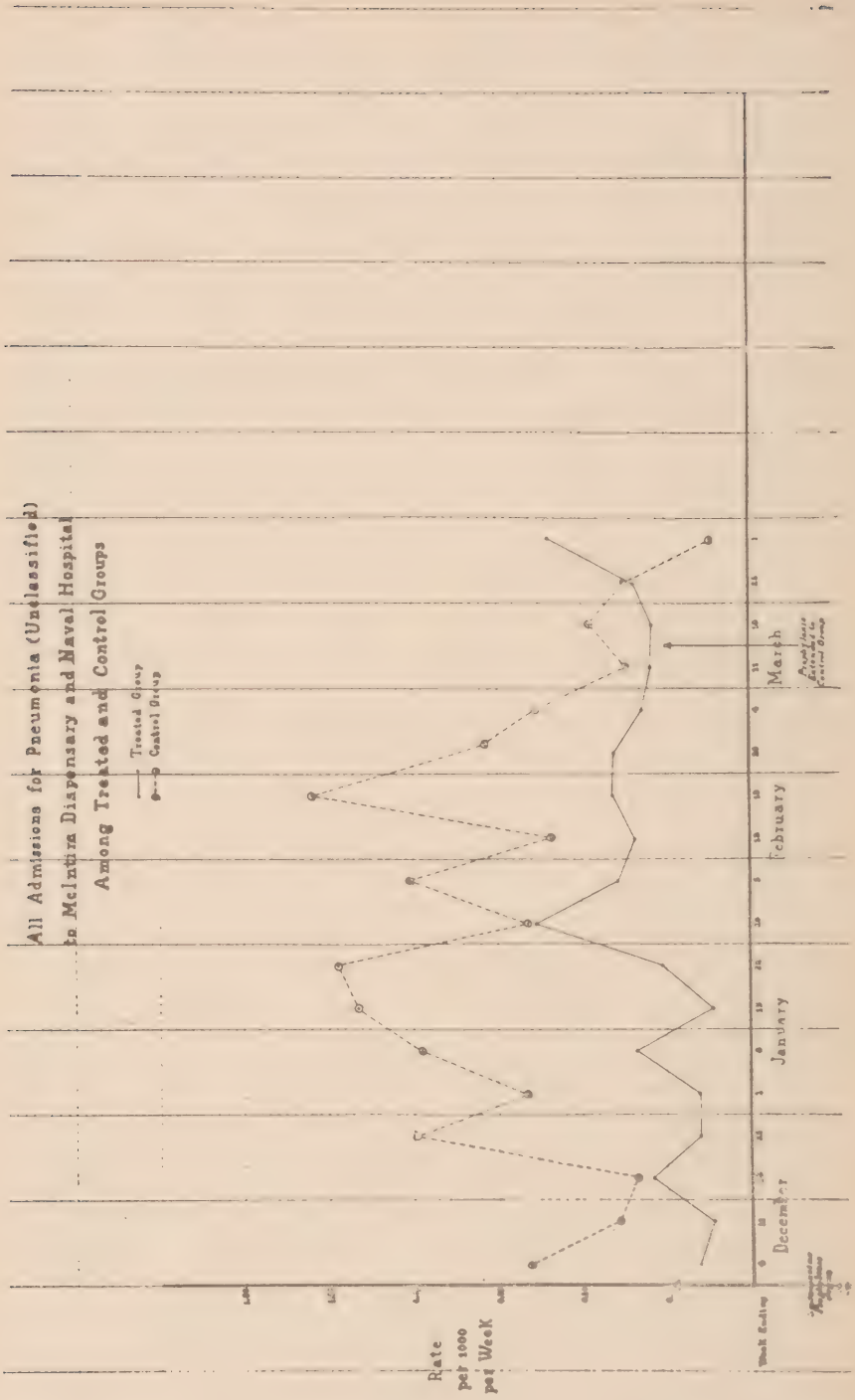

All Admissions for Pneumonia (Unclassified)
in Malaria Dispensary and Naval Hospital
Among Treated and Control Groups
Treated Group
Control Group
Rate
per 1000
per Week
December
January
February
March

CHART 18

Cerebro-Spinal Fever (meningococcic)
at U. S. N. T. S., Great Lakes, Illinois
1943 and 1944

Number of Cases, Rates per 1000 per Month
and Bar Graph of Rates

Control		Month and Year	Treated (Treatment began Dec. 1, 1943)	
Rate	Number		Number	Rate
0.00	0	Jan. '43	2	0.10
0.10	2	Feb. '43	3	0.15
0.05	1	Mar. '43	15	0.75
0.64	8	Apr. '43	8	0.40
0.43	5	May '43	21	1.06
0.32	4	June '43	9	0.45
0.08	1	July '43	6	0.30
0.32	4	Aug. '43	4	0.20
0.08	1	Sept. '43	1	0.05
0.00	0	Oct. '43	1	0.05
0.16	2	Nov '43	2	0.10
0.43	5	Dec. '43	0	0.00
0.64	7	Jan. '44	0	0.00
1.00	11	Feb '44	0	0.00
0.32	4	Mar '44	0	0.00

Graphic Portrayal of Rate

Graphic Portrayal of Rate

Sulfadiazine Prophylaxis Begun in Treated Group

TABLE 12.—*Disease rates in recruit camps for December 1943, January and February 1944*

Disease	Total cases		Rate/1000	
	Treated *	Untreated	Treated	Untreated
Upper respiratory complaints at sick call	40,363	25,599	595	704
Admitted to dispensaries with upper respiratory infections	2,886	3,897	42.7	107
Admitted to hospital with all respiratory infections	398	2,621	5.9	72.0
Scarlet fever	84	441	1.2	12.1
Tonsillitis or pharyngitis	601	2,145	8.9	59.1
Pneumonia, lobar or broncho	99	154	1.5	4.2
Cerebrospinal fever (mening.)	2	24	0.0	0.7
Rheumatic fever	10	51	0.1	1.4
Otitis media, acute	119	369	1.8	10.1
Sinusitis, acute	38	81	0.6	2.2

* Treated signifies groups receiving prophylaxis; untreated signifies control groups receiving *no* prophylaxis. This terminology is used throughout these tables.

TABLE 13.—*Disease rates in service school for December 1943 and January 1944*

Disease	Total cases		Rate/1000	
	Treated	Untreated	Treated	Untreated
Upper respiratory complaints at sick call	2,042	7,225	274	838
Admitted to dispensaries with upper respiratory infections	60	419	8.1	48.5
Admitted to hospital with all respiratory infections	128	697	17.2	80.8
Scarlet fever	36	216	4.8	25.0
Tonsillitis or pharyngitis	27	265	3.6	30.7
Pneumonia, lobar or broncho	1	29	0.1	3.4
Cerebrospinal fever (mening.)	0	6	0.0	0.7
Rheumatic fever	8	38	1.1	4.4
Otitis media, acute	33	118	4.4	13.7
Sinusitis, acute	4	5	0.5	0.6

CHART 19

Admissions for Rheumatic Fever to
McIntire Dispensary and Naval Hospital
Among Tropical and Control Groups
Tropical Group
Control Group
Rate
per 1000
per Week
December
January
February
March
April

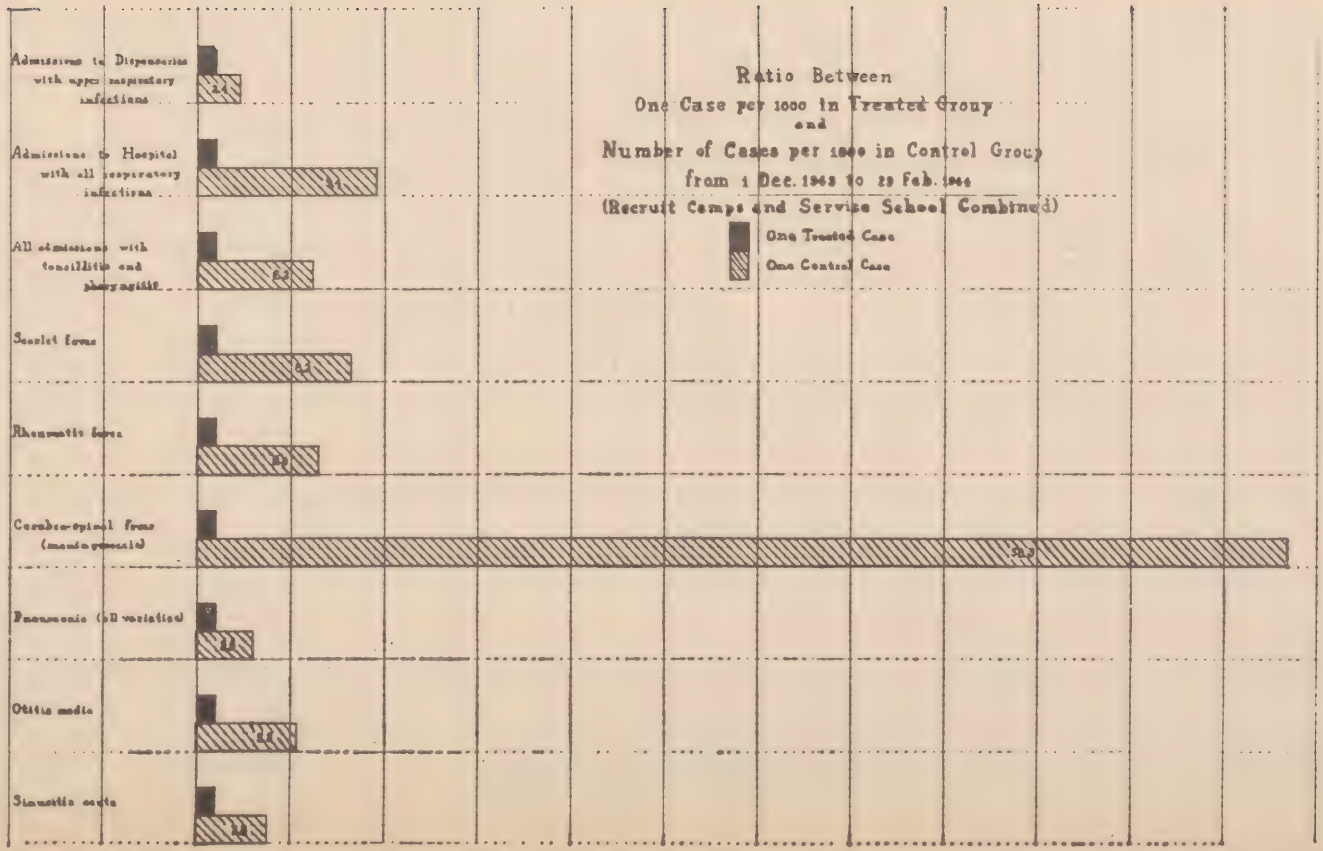

Ratio Between
One Case per 1000 in Treated Group
and
Number of Cases per 1000 in Control Group
from 1 Dec. 1943 to 29 Feb. 1944
(Recruit Camps and Service School Combined)
One Treated Case
One Control Case
Admissions to Dispensaries with upper respiratory infections
24
Admissions to Hospital with all respiratory infections
44
All admissions with tonsillitis and pharyngitis
42
Scarlet fever
44
Rheumatic fever
29
Cerebro-spinal fever (meningococcic)
523
Pneumonia (all varieties)
11
Otitis media
22
Sinusitis acute
11

CHART 20

tive for beta hemolytic streptococci, and that 45.8 percent of 162 men with catarrhal fever not taking prophylactic sulfadiazine had positive cultures.

Effect of Prophylactic Sulfadiazine on Incidence of Pneumonia

Practical considerations have made separation of pneumonia into virus and bacterial etiology difficult. As a result, all pneumonia cases have been grouped together, regardless of their etiology. For every case occurring in a treated recruit there were 2.8 cases among the untreated recruits. The results are similar in the Service School. Chart 17 shows the weekly incidence in the recruit camps and Service School.

Effect of Prophylactic Sulfadiazine on Incidence of Cerebrospinal Fever (Meningococcic)

In this disease sulfadiazine as a prophylactic agent was most successful. During the period under discussion there were 3 cases of meningitis among the treated groups as compared with 32 cases among the control groups. Careful questioning of the 3 patients revealed that only 1 of the patients had received any sulfadiazine, and this man's blood sulfonamide level was less than 0.2 mg. percent. This difference is emphasized when these absolute numbers of cases are reduced to rates, because the treated groups are approximately twice as large as the control groups (chart 18).

Effect of Prophylactic Sulfadiazine on Incidence of Rheumatic Fever

Because of the antecedent role of the streptococcus in the causation of rheumatic fever, it is clear that the complete effect on the incidence of rheumatic fever will not be evident until some subsequent date. Despite this, for each case occurring among the treated recruits there have been 14 among the untreated. Chart 19 shows the weekly course of rheumatic fever incidence at the Training Center during the period under discussion.

Tables 12 and 13 summarize the incidence of the diseases previously mentioned and the number of hospital and dispensary admissions in the treated and untreated groups. Chart 20 is a graphic presentation of these values.

Laboratory Studies

Observations on Blood Sulfadiazine Levels.—A blood sulfadiazine level was obtained for each patient admitted to the dispensaries and hospital with any respiratory infection. A group of healthy men receiving sulfadiazine prophylactically was used to obtain control blood levels. Table

14 shows the relationship between the number of positive throat cultures and blood sulfadiazine levels in the treated group. If one divides the number of positive throat cultures by the total number of throat cultures at a given blood sulfonamide level, it becomes evident that the percentage of positive throat cultures is not related to that level.

TABLE 14.—*Incidence of positive (hemolytic streptococcus) throat cultures in relation to sulfadiazine blood level in men admitted to dispensaries for upper respiratory infections*

Sulfadiazine blood level Mg. percent	Service school			Green Bay area		
	Negative	Positive	Total	Negative	Positive	Total
0.0–0.2	49	15	64	595	77	672
0.2–0.4	0	1	1	21	0	21
0.4–0.6	9	4	13	102	18	120
0.6–0.8	5	1	6	112	8	120
0.8–1.0	13	1	14	139	7	146
1.0–1.2	6	0	6	126	5	131
1.2–1.4	12	2	14	170	11	181
1.4–1.6	3	1	4	218	7	225
1.6–1.8	3	2	5	204	11	215
1.8–2.0	4	0	4	159	8	167
2.0–2.2	7	2	9	180	7	187
2.2–2.4	7	0	7	141	9	150
2.4–2.6	7	2	9	139	11	150
2.6–2.8	2	0	2	96	2	98
2.8–3.0	1	1	2	64	5	69
3.0–3.2	7	1	8	87	7	94
3.2–3.4	3	0	3	51	3	54
3.4–3.6	5	0	5	32	3	35
3.6–3.8	5	1	6	29	1	30
3.8–4.0	2	0	2	15	2	17
4.0–4.2	4	0	4	28	2	30
4.2–4.4	0	0	0	14	1	15
4.4–4.6	0	0	0	9	1	10
4.6–4.8	0	0	0	4	0	4
4.8–5.0	1	1	2	2	0	2
5.0–5.2	0	0	0	6	0	6
5.2–5.4	0	0	0	1	0	1
5.4–5.6	1	0	1	2	0	2
5.6–5.8	0	1	1	2	0	2
5.8–6.0	0	0	0	0	0	0
6.0–6.2	0	0	0	3	0	3
6.2–6.4	0	0	0	0	0	0
6.4–6.6	0	0	0	3	0	3
6.6–6.8	1	0	1	0	0	0
6.8–6.0	0	0	0	0	0	0
6.0–7.2	0	0	0	0	0	0
7.2–7.4	0	0	0	1	0	1
Total	157	36	193	2,755	206	2,961

Table 15 demonstrates the mean, median, standard deviation, and range of the blood sulfadiazine levels obtained in patients and in well men receiving sulfadiazine prophylactically. There was no significant difference in the means of these groups. It can be concluded, therefore, that a low blood sulfadiazine level was not the important factor in the failure of sulfadiazine prophylaxis in these men studied, if we assume that the blood level at the time of admission accurately reflects the blood level at the time the infection was contracted.

In an effort to determine whether there was an accumulation of sulfadiazine in the blood after prolonged administration, the blood sulfadiazine levels were studied in successive groups who had been receiving the drug for 1, 2, 3, 4, and up to 31 days. Chart 21 shows the high, mean, and low levels. It can be seen that there is no accumulation of sulfadiazine in the blood after 1 month of administration, and that the highest levels are reached as early as the second day. It is also shown that the range between high and low levels is considerable. It is possible that an occasional man might have taken more or less than the prescribed dose; this would account in part for the wide range in blood levels. Undoubtedly, there is individual variation in the absorption and excretion of the drug.

TABLE 15.—*Comparison of blood sulfadiazine levels in patients who contracted respiratory infections and in men who remained well while taking prophylactic sulfadiazine*

Subjects tested	Number of observations	Mean Mg. %	Median Mg. %	Standard deviation Mg. %	Range Mg. %
Green Bay patients	2,961	1.5	1.5	1.1	0.0–7.4
Service School patients	193	1.4	0.9	1.4	0.0–6.8
Well men	56	1.7	1.9	1.1	0.0–4.0

TABLE 16.—*Summary of throat cultures taken from men admitted to dispensaries and hospitals for upper respiratory infections*

Subjects	Positive		Negative		Total
	Number	Percent	Number	Percent	
Treated	242	7.7	2,912	92.3	3,154
Controls	178	52.3	162	47.7	340

CHART 21

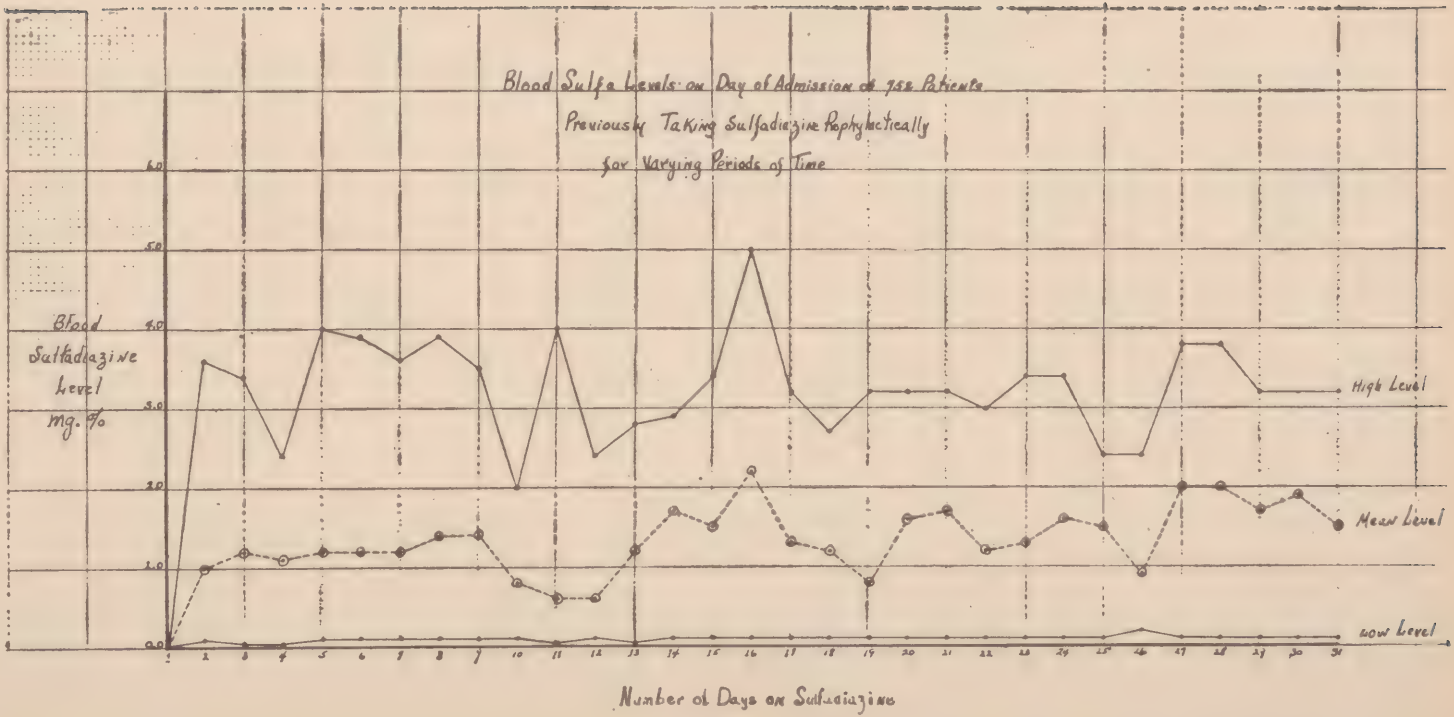

Blood Sulfa Levels on Day of Admission of 752 Patients
Previously Taking Sulfadiazine Rophylactically
for Varying Periods of Time
Blood Sulfadiazine Level mg. %
6.0
5.0
4.0
3.0
2.0
1.0
0.0
High Level
Mean Level
Low Level
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
Number of Days on Sulfadiazine

TABLE 17.—*Streptococcus typings according to type and week*

Type	December week ending				January week ending					February week ending				March week ending			Total
	4	11	18	25	1	8	15	22	29	5	12	19	26	4	11	18	
1	1	0	6	0	4	0	5	4	6	6	3	2	3	3	0	0	43
2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
3	0	1	5	3	11	3	2	11	9	6	0	2	1	7	0	0	61
5	1	5	6	1	2	3	3	2	6	5	3	3	2	7	0	0	49
6	0	1	2	2	3	4	0	3	0	3	0	1	0	1	0	0	20
9	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
12	0	0	2	1	0	0	1	1	1	0	0	0	1	0	0	0	7
15	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	2
17	1	8	4	5	6	6	1	8	6	4	1	4	3	7	0	0	67
18	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
19	0	5	5	1	3	1	2	13	5	12	5	0	1	11	0	0	55
24	0	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	4
26	0	0	1	0	1	0	0	0	1	1	2	0	0	0	0	0	6
30	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	2
32	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	2
33	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
36	0	0	0	0	1	1	0	0	0	2	0	1	0	0	0	0	5
39	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	2
41	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
43	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
44	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
46	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Total	3	23	34	13	35	20	15	44	34	41	17	14	13	27	0	0	333

TABLE 18.—*Streptococcus typings according to regimental areas December, January, February, and March*

Type	Number of regimental area									Service school and O. G. U.	Total
	21st	23d	25th	27th	29th	31st	8th	10th	12th		
1	4	0	2	7	3	3	4	1	1	18	43
2	0	0	0	0	0	1	0	0	0	0	1
3	1	2	9	6	2	2	11	5	3	16	61
5	5	5	7	11	1	1	0	0	1	10	49
6	3	1	1	4	0	0	0	6	2	6	20
9	0	1	0	0	0	0	0	0	0	0	1
12	2	0	0	1	2	0	0	0	0	2	7
15	0	0	1	0	0	0	0	0	0	1	2
17	3	9	7	10	1	2	3	6	5	21	67
18	0	0	0	0	0	0	0	0	0	1	1
19	2	2	4	1	1	4	8	4	1	28	55
24	0	0	0	1	0	1	0	0	0	2	4
26	1	0	0	1	0	0	1	0	0	0	6
30	0	0	0	0	0	0	0	0	0	2	2
32	0	0	0	0	0	0	0	0	0	2	2
33	0	0	0	0	1	0	0	0	0	0	1
36	0	0	0	0	1	0	0	0	0	4	5
39	0	0	0	0	0	0	1	1	0	0	2
41	0	0	0	0	0	1	0	0	0	0	1
43	0	1	0	0	0	0	0	0	0	0	1
44	0	0	0	0	0	0	1	0	0	0	1
46	0	0	0	0	0	0	0	0	0	0	1
Total	21	21	34	50	12	15	31	13	18	113	333

Observations Regarding Throat Cultures.—A throat culture on blood agar was taken of all the patients with respiratory infections admitted to the dispensaries and hospital. Control cultures were taken of a series of upper respiratory admissions in the control camps. Table 16 demonstrates the remarkable reduction in the percentage of positive beta hemolytic streptococcus throat cultures in the treated men as compared with the controls. An analysis of all group A typings completed to date is shown in tables 17, 18, and 19.

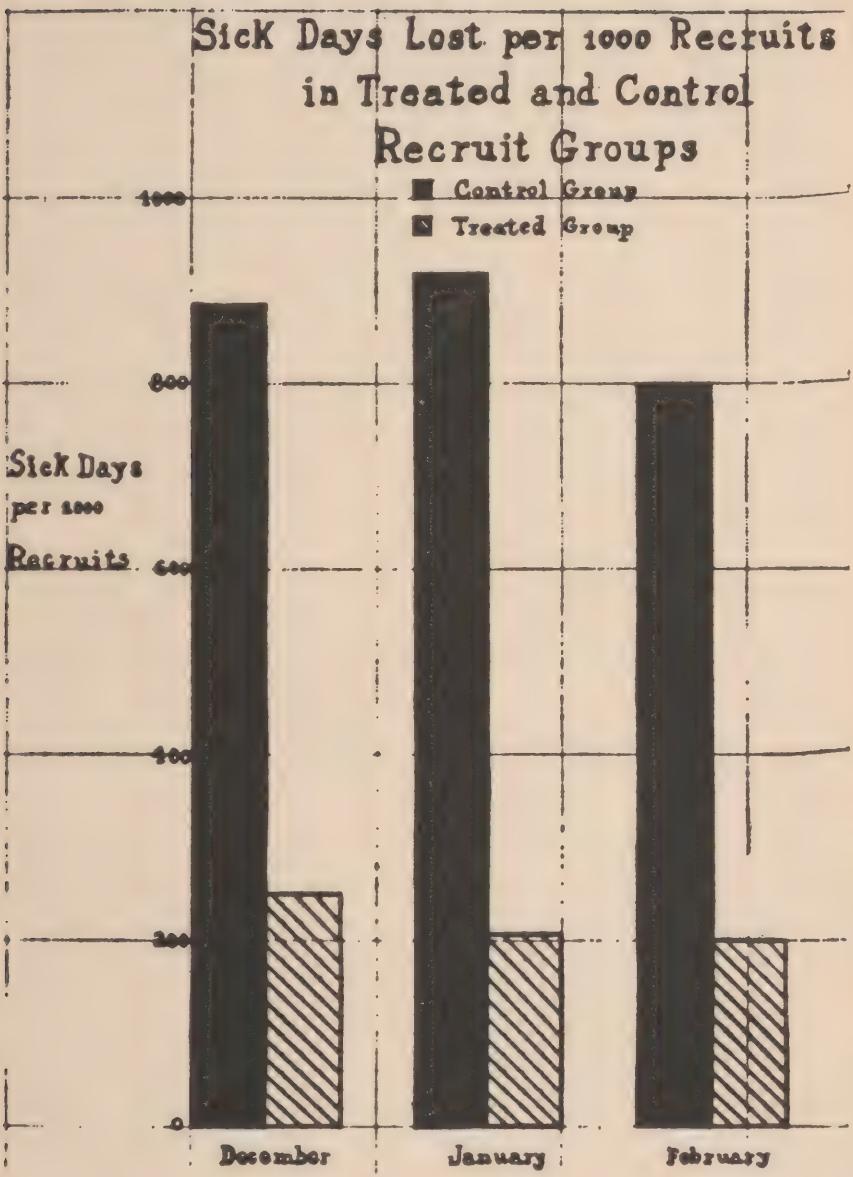
Types 17, 19, 3, 5, 1, and 6 were most frequently isolated in the order named. Type 17, which was most prevalent, occurred 67 times or in 20 percent of the entire group.

It becomes apparent that a large number of types have been endemic throughout the entire station and throughout the entire period of time indicated. No one type has reached epidemic proportions. It is to be seen that any of the commonly isolated types has been found in association with a wide variety of clinical entities. In this analysis it is assumed that all types of streptococci are grown, isolated, and typed with equal facility.

TABLE 19.—*Streptococcus typings according to diagnosis, Green Bay, service school, and controls, December, January, February, and March*

Type of Group A hemolytic streptococcus	Diagnoses		
	Scarlet fever	Pharyngitis and tonsillitis	Catarrhal fever
1	1	26	13
2		1	
3	2	28	25
5		17	22
6		11	8
9			1
12		2	3
15		2	
17	4	24	33
18			1
19	2	22	26
24		2	2
26		2	2
30		2	
32			2
33			1
36		3	2
39		1	1
41			1
43			1
44		1	
46			1

CHART 22


Sick Days Lost per 1000 Recruits in Treated and Control Recruit Groups
Control Group
Treated Group
Sick Days per 1000 Recruits
1000
800
600
400
200
0
December
January
February

An Estimation of Number of Man-Days Saved as Result of Institution of Sulfadiazine Prophylaxis Program

The actual number of sick days spent in the wards of the dispensaries and hospital from 1 December 1943 to 29 February 1944 was counted for both the treated and untreated men. By subtracting these two figures and assuming the same morbidity rate for the two groups, and correcting for the difference in populations, an estimation was made of the man-days saved.

By using the aforementioned method, it has been estimated that 45,359 man-days were saved from 1 December 1943 to 29 February 1944 by the sulfadiazine streptococcus prophylaxis program. Chart 22 graphically represents the number of sick days lost per thousand recruits in the treated and control groups for December, January, and February. It is seen that for every 1 man-day lost in the treated group, there were more than 4 man-days lost in the control group.

For this same period, 384 man-days have been lost from untoward sulfadiazine reactions. Calculated from Bureau of Medicine and Surgery data on the average time spent on the Sick List because of respiratory infections and their sequelae, our saving during this controlled study totals 72,776 man-days.

Untoward Reactions: Dermal Reactions in White Enlisted Personnel

From 1 December 1943 to 31 March 1944 inclusive, a total of 654 dermal reactions was observed among the white enlisted personnel who were taking prophylactic sulfadiazine. Of these, 466 were seen in recruits in the Green Bay area giving a rate of 5.6 per thousand, and 43 were observed among enlisted personnel in Service School giving a rate of 1.5 per thousand. The men in Green Bay area and part of the men in Service School were on the program during most of the prophylaxis period. These 2 groups thus give the most accurate reaction rates. The remaining rashes occurred in men who were on the program for only 2½ weeks, and these have not been included in the computation of the rates.

To identify true sulfadiazine reactions more clearly, all men except those who have been transferred were retested with sulfadiazine at a later date. To retest, after the initial reaction, the men were not given sulfadiazine for a period of from 7 to 21 days, and they were then given 0.5 gm. or 1 gm. of sulfadiazine daily for 3 days under close observation. When secondary reactions occurred, the time of onset and type of reaction were noted, and the men were permanently removed from the program. If no secondary reactions occurred, the men were again included in the program and no subsequent reactions were observed. A summary of the dermal reactions observed in enlisted personnel is given in table 20.

TABLE 20.—*Dermal reactions in white enlisted personnel*

Primary type of reaction	All reactions		Total Number retested	Retested				Secondary reaction types on retesting						
				With reactions		Without reactions		Erythematous	Papular	Urticarial	Photosensitization	Morbilliform	Fixed eruption	Unclassified
	Number	*Percent*		*Number*	*Percent*	*Number*	*Percent*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*	*Number*
Morbilliform	253	38.7	155	79	51	76	49	52	5	8	0	7	0	7
Erythematous	148	22.6	85	38	45	47	55	35	0	1	0	0	0	2
Urticarial	140	21.4	92	3	3	89	97	1	0	2	0	0	0	0
Papular	85	130	63	27	43	36	57	16	8	0	0	1	0	2
Photosensitization	15	2.3	10	9	90	1	10	0	0	0	9	0	0	0
Fixed eruption	6	0.9	2	2	100	0	0	0	0	0	0	0	2	0
Exfoliative dermatitis	5	0.8	0	0	0	0	0	0	0	0	0	0	0	0
Purpura	2	0.3	0	0	0	0	0	0	0	0	0	0	0	0
Total	654	100.0	407	158		249		104	13	11	9	8	2	11

A primary dermal reaction is defined as the initial reaction observed while prophylactic sulfadiazine is being given. Primary dermal reactions are classified as (a) morbilliform; (b) erythematous; (c) urticarial; (d) papular; (e) photosensitization; (f) fixed eruption; (g) exfoliative dermatitis; (h) purpura.

Morbilliform Reactions.—Morbilliform reactions were by far the most common dermal reactions as they made up 38.7 percent of the total primary rashes. The typical eruption of this type is fine morbilliform rash more or less generalized except for the face, and showing confluent lesions over the back and extensor surfaces of the extremities. Only about one-third of the cases have involvement of the face. In some cases, the rash is more generally confluent, even over the trunk, with only small scattered clear areas intervening. In a few instances, the rash involves solely the extremities, or shows sparse lesions only on the trunk. This rash closely resembles German measles with which it is easily confused. When the rash is blotchier and confluent and accompanied by fever, the differentation from "red" measles is sometimes difficult. The most characteristic feature of these rashes is the bright vivid pink of the lesion as contrasted with duller red lesions of measles and German measles. Other features usually present are a moderate generalized lymphadenopathy, mild temperature elevation of 99° F. to 101° F., pruritis, a facial flush, and injected conjunctivae. Because the rash sometimes cannot be conclusively differentiated from German measles the following helpful diagnostic points are offered:

1. The bright vivid pink color of the lesions.
2. The face is not usually involved.
3. There is frequent temperature elevation above 100° F. which is uncommonly seen in German measles.
4. The postauricular glands are rarely as large as in German measles.
5. There is frequent predominance and confluence of the lesions on the extensor surfaces of the extremities.
6. There is frequent pruritis.
7. The entire rash usually appears simultaneously. In German measles, the rash typically appears on the face and spreads downward progressively. This is a helpful point when the rash involves the face. In doubtful cases, isolation of the patient in sickbay for a few hours to observe progression of the lesions was found to be helpful.

As for the differentiation from measles, these are the most reliable diagnostic points:

1. There is no preceding history of coryza and cough.
2. There is an absence of Koplik's spots.
3. Conjunctival injection is common but coryza and photophobia are rare.
4. The lesions are pink.

5. There is no downward progression of lesions.
6. Pruritis is present.
7. Temperature elevations from 102° F. to 104° F., as seen in measles, are uncommon.

The rashes develop within an average period of 15 days of sulfadiazine prophylaxis. The range was from 1 to 40 days, although the majority of cases occurred consistently in the 7 to 21 day period.

Erythemas.—The erythematous eruptions comprised 22.6 percent of the total primary rashes. The erythemas were generally of 4 different types. The mildest type is a fine red macular rash involving mainly the trunk. The second type is a blotchy erythema scattered mainly over the trunk and sometimes over the extremities. The third type, a rather uncommon one, is characterized by discrete circular bright red macules, varying from 1 cm. to several centimeters in diameter, which are scattered over both the trunk and extremities. The last and most severe type is a diffuse erythema, usually covering the face, trunk, and extremities. As may be seen, the erythemas have a predilection for the trunk, but, with increasing severity, spread to the extremities and face as well. Concomitant features, especially in the diffuse erythemas, are a sudden onset, acute prostration, chills, intensely injected conjunctivae, a diffusely injected pharynx, injected tympanic membranes, and frequent temperature elevations to 102°-103° F. and higher.

These types of reactions, particularly in diffuse erythemas, must be differentiated from scarlet fever. Desquamation has been observed in some of the more severe erythemas from sulfadiazine. Because some of the scarlet fever patients may be treated with sulfonamides, it is imperative to make a correct diagnosis. Differentiating characteristics of sulfadiazine erythemas are as follows:

1. Sore throat, rare.
2. Intense conjunctival injection.
3. Intense facial erythema and absent circumoral pallor.
4. Erythema is diffuse and not punctate in character.
5. No predilection for the folds or thin-skinned areas. The rash often is less intense over these areas.
6. Absence of punctate appearance of the soft palate and uvula.

The average period of time under sulfadiazine treatment before the rash developed was 13 days with a range of from 5 to 21 days.

Urticarias.—Urticarias comprised 21.4 percent of the total rashes observed. There was nothing characteristic either in type or distribution to differentiate them from urticarias from other causes. They were sometimes associated with nasal coryza and edema of the hands, face, or feet. As usual, they were markedly pruritic and not associated with fever. Some of the morbilliform and papular rashes had scattered areas

of urticaria as well. Adrenalin or ephedrine sulfate usually relieved the rash and symptoms.

These men had been taking sulfadiazine for an average period of 16 days with a range of from 1 to 56 days. There was wide variation between individual cases in the length of time that sulfadiazine was taken.

Papular Rashes.—The papular rashes constituted 15 percent of the total rashes. These rashes are of 2 distinct types and are the most easily diagnosed of the sulfadiazine eruptions. One type is bright pink and the other, deep red. The lesions vary in size from 1 mm. to 2 mm. to confluent areas of several centimeters in diameter; they are irregular in outline, and are scattered usually over both trunk and extremities. The confluent areas are common over the upper part of the chest and back, and especially, over the extensor surfaces of the extremities. In the recruits, the lesions over the areas covered by boots are often purpuric, presumably from pressure. Pruritis is frequently intense. About half the men had temperatures of from 99° F. to 101° F.

The men were taking sulfadiazine for an average period of 13 days with a range of from 5 to 25 days. Most of the cases fell within the 13-day period.

Photosensitization.—There have been observed 15 cases, or 2.3 percent of the total, in which the skin manifestations appeared only in areas exposed to sunlight, such as the face, neck, and the dorsa of the hands and wrists. These are thought to be examples of photosensitization. In general, the rashes are either erythematous or of a pink papular type. In all cases there were facial rashes and in two-thirds similar involvement of the dorsa of the hands and wrists as well. There is usually an associated edema, burning sensation, and pruritis of the areas concerned. Those patients with erythema had secondary exfoliation.

These patients had been taking prophylactic sulfadiazine for an average period of 16 days with a range of from 2 to 28 days.

Fixed Eruption.—These rashes (six) formed 0.9 percent of the total reactions. All patients gave histories of reactions over the same areas from previous sulfonamide therapy. Apparently, the previous sulfonamides caused local increased tissue sensitivity, so that on subsequent sulfadiazine ingestion a rash occurred at the same sites. Two of the patients had been treated with local sulfathiazole ointment for burns on the forearms and one for impetigo of the face. These three developed a local sulfathiazole dermatitis over the same areas at that time. The other three patients had been taking either sulfathiazole or sulfadiazine orally, and developed localized scattered eruptions over the trunk and extremities. All six patients reacted again within a few hours after the initial gram of sulfadiazine on the streptococcus program.

Fixed eruptions are either of a papular, erythematous, or eczematoid nature. There are probably more fixed eruptions than are generally

TABLE 21.—*Summary of data in cases of exfoliative dermatitis*

Number	Race	Age	Grams of drug before admission	Sulfadiazine blood level on admission	Sulfonamide received after admission	Hospital days	Outcome
1	White	18	35	Not tested	Sulfadiazine, 7 grams	14	Died.
2	White	22	21	1.6 mg. %	None	6	Died.
3	White	18	20	1.2 mg. %	Sulfathiazole 7 grams	6	Died.
4	Negro	18	14	1.1 mg. %	Sulfathiazole 5 grams	27	Recovered.
5	Negro	18	16	Not tested	None	26	Recovered.
6	Negro	17	14	Not tested	None	29	Recovered.
7	White	35	37	Not tested	None	69	Recovered.
8	White	19	28	Not tested	None	64	Recovered.

TABLE 22.—*Dermal reactions in Negro enlisted personnel*

Type of reaction			Retested with reaction		Retested without reaction		Not retested	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Erythematous	15	40.5	5	33	8	53	2	14
Papular	11	29.8	2	18	8	73	1	9
Morbilliform	4	10.8	1	25	2	50	1	25
Urticarial	3	8.1	1	33	2	67	0	0
Exfoliative dermatitis	3	8.1	0	0	0	0	3	100
Fixed eruption	1	2.7	1	100	0	0	0	0
Total	37		10		20		7	

recognized. It was observed that some of the men retested developed secondary lesions at the sites of pigmentation residual from the primary lesions. These, however, were not included as fixed eruptions.

Generally, therefore, fixed eruptions represent local tissue hypersensitivity which is manifested by secondary reactions within a few hours. The duration of this hypersensitivity is not known. In this series, the first reactions occurred in from 2 to 18 weeks before the secondary cases.

Exfoliative Dermatitis.—For convenience, the five cases of exfoliative dermatitis occurring in the white and the three cases occurring in the Negro personnel are considered together. Table 21 shows the salient clinical and laboratory features.

Table 21 shows that two out of three patients who received sulfadiazine therapy after the appearance of skin manifestations died. Four out of five of the men who were treated only with supportive measures made a complete recovery.

Because of the wide variation in the presenting signs and symptoms in cases that subsequently proved to be exfoliative dermatitis, the following admission diagnoses at the hospital were made: catarrhal fever, chickenpox, German measles, and scarlet fever.

The original skin lesions rapidly progressed to secondary vesicles and bullae which coalesced. Subsequent to this, a more or less generalized exfoliation of the skin and mucous membranes occurred. In addition, there were an acute febrile course, purulent conjunctivitis, purulent nasal discharge, and necrotic sloughing lesions of the lips, mouth, and throat. The leukocyte counts were usually increased and a hypochromic anemia often developed. Therapy included plasma and whole blood transfusions, intravenous saline and dextrose solutions, penicillin, and minute attention to the local lesions.

Purpura.—Only two cases of eruptions with a considerable purpuric component were seen. Fairly marked purpura developed in the lesions of a previous maculopapular rash over the trunk and extremities, the purpura coming 1 or 2 days after the original rash. There were, however, many cases in which small petechial hemorrhages or mild purpura occurred with rashes which were predominantly of another type. Such purpuras were common over areas of pressure, such as over the areas covered with the boots.

Dermal Reactions in the Negro Enlisted Personnel

A summary of these dermal reactions is in table 22. Although there was a relatively high incidence of exfoliative dermatitis, the absolute number of reactions among Negro enlisted personnel was small. Because this group had been taking prophylactic sulfadiazine for only 2½ weeks, no conclusions can be drawn.

TABLE 23.—*Summary of data in 5 cases of granulocytopenia*

Case	Age	Race	Grams of drug before symptoms (1.0 gm. daily)	Grams of drug before admission to hospital	Admission physical findings	Admission WBC	Admission blood smear	Admission blood sulfonamide Mg. ¼	Treatment	Outcome
W. N.	29	W	24	38*	Bilateral pneumonitis, red throat.	1,000	100% lymphs.	2.2	Transfusions, pentnucleotide, penicillin.	Died.
F. W.	24	W	33	40**	Grayish tonsillar exudate.	1,100	100% lumphs.	3.3	Same	Died.
R. P	30	W	15	19***	Yellow patches on tonsils.	800	100% lymphs.	0.1	Same	Died.
H. K.	29	W	42	42†	Pharynx injected, spleen enlarged.	2,600	60% lymphs. 38% monos. 2% sets..	?	Transfusions, pentnucleotide.	Lived.
H. S	20	C	8	8††	White tonsillar exudate.	5,800	Not done		Transfusions, pentnucleotide.	Lived.

* Patient inadvertently received 45 gm. of sulfadiazine during first week of his hospitalization

** Patient received 14 gm. of sulfadiazine during the first 2 days of hospitalization.

*** Patient had not received any sulfadiazine for 6 days prior to his admission to McIntire, because he was believed to have a drug fever from therapeutic sulfadiazine while in the sickbay where he was undergoing treatment for catarrhal fever.

† While this patient was returning to camp following "boot" leave (7 days after last dose of sulfadiazine), he experienced malaise, fever, and slight sore throat. Two days later he was admitted to McIntire.

†† Because an admission diagnosis of acute tonsillitis had been made, sulfadiazine was instituted: 14 gm. A leukocyte count at that time was 2300, with 42 segmented forms 7 bands, 47 lymphocytes, and 4 monocytes.

Up to date there have been six cases of granulocytopenia, four of which were fatal. Of the four fatal cases, three were studied in the wards, and one patient died at home while on "boot" leave. Unfortunately, the circumstances of the death in the last case were not obtainable. Table 23 shows the salient clinical and laboratory features in the three fatal cases of granulocytopenia and in the two cases in which the patients recovered. These five cases presented several interesting features: There was no patient under the age of 20; the amount of sulfadiazine received was not large in any case; the blood sulfadiazine level in no case reached unusual levels. It is to be noted that three of the five patients received varying amounts of sulfadiazine in addition to the regular 1 gm. daily prophylactically.

At the beginning of the program no examinations of white cell counts and of urine specimens were made. Subsequent events have shown that even such a small dose as 1 gm. a day can have a suppressing action on the leukocytes. Because of this, it was decided to take a sampling of leukocyte counts among men who had been receiving prophylactic sulfadiazine longer than 3 weeks. At the same time it was decided to examine a similar number of urine specimens microscopically for hematuria. A total of 650 leukocyte counts and urinalyses were done among the white recruits, and 250 leukocyte counts and urinalyses among the Negro recruits. The results of the blood sampling appear in table 24.

The question arises whether these differences between the leukocyte counts of white and Negro patients are racial or due to a greater sensitivity on the part of the Negro to the leukocyte-suppressing action of sulfadiazine. In an effort to answer this question, leukocyte counts were taken of a random sample of 125 Negroes on first reporting at the Training Center for duty, before receiving any sulfadiazine. These Negroes had a wide distribution in respect to age (range 17 to 36 years), degree of racial mixture, home state, and occupation. The mean of these counts was 6,940, and the distribution was as follows:

	Percent
Above 10,000	1.6
5,000-10,000	89.6
4,000-5,000	8.0
Under 4,000	0.8

Two Negroes and one white man were found to have a leukocyte count below 4,000. In all three cases the suppression occurred mainly in the granulocytic series. Each man was immediately withdrawn from the program. After 3 days, one attained a normal count; after 7 days, the second had a normal count; there is no information for the third person since he was on "boot" leave soon after the discovery of leukopenia.

There has been no case of hematuria without associated evidence of urinary tract infection in the 900 urine specimens examined.

Unclassified Reactions

These 20 cases of unclassified reactions, representing 3 percent of the total, were reactions other than dermal or hematopoietic. A list of these reactions includes:

Fairly Common	chills fever pruritis flushed face burning eyes with conjunctival injection cyanosis of hands (although commonly observed, this is not considered an untoward reaction)
Less Common	edema of hands, feet, or face headache anorexia vertigo
Rare	arthralgia nausea vomiting backache sore throat with pharyngeal injection coryza mild asthma

TABLE 24.—*Leukocyte counts in white and Negro recruits receiving prophylactic sulfadiazine*

	Whites	Negroes
Total number of counts	650	250
Average (mean)	8,064	7,138
Percent above 10,000	13.1	9.2
Percent between 5,000 and 10,000	82.9	79.2
Percent below 5,000	4.0	11.6
Percent below 4,000	0.15	0.8

One case of jaundice was seen. A 21-year-old Negro, who had been taking prophylactic sulfadiazine for 2 weeks, negligently omitted the drug for 1 week and became acutely ill with chills, fever, and urticaria 6 hours after the ingestion of 1 gm. of sulfadiazine. He subsequently developed nausea, vomiting, facial edema, jaundice, an enlarged liver, and a vesicular rash of the face. After a hospital course of 4 weeks, he is apparently recovering. The etiologic agent of the liver disturbance is not definite, although prophylactic sulfadiazine cannot be excluded.

Sensitivity and Retesting for Sensitivity

Table 20 shows the frequency of secondary reaction types elicited by retesting. Secondary reaction is defined as a reaction appearing on re-

testing. There are five important clinical facts that can be derived from the secondary dermal reactions:

1. The secondary erythematous rashes were by far the most common secondary dermal reactions as they constituted almost two-thirds of the total.

2. Exclusive of the secondary morbilliform rashes, the other secondary dermal reactions occurred within an average period of 4 hours after the initial retest dose. The range was from 1 to 10 hours.

3. The secondary morbilliform rashes apparently developed more slowly as the average reaction time was 18 hours (range from 5 to 36 hours) after the first retest dose.

4. Urticarias seem to be an uncommon type of reaction to sulfadiazine, as only 3 of 92 primary urticarias had secondary reactions on retesting.

5. The secondary morbilliform and papular rashes all had primary rashes of either of these two types. None had primary erythemas or urticarias.

Unclassified secondary reactions were essentially the same as those described previously under that heading.

Of the 249 men who were retested without secondary reactions, many were thought to have true primary drug reactions. There are several possible explanations. First, during the 3-week period when 0.5 gm. of sulfadiazine was used as a retest dose, only 8 of 58 men (14 percent) gave a secondary reaction; whereas during the period when 1 gm. of sulfadiazine was used, 154 or 356 men (43 percent) reacted positively. It can be seen, therefore, that the size of the test dose is a factor in the development of secondary reactions. Second, it is also possible that in some of the men who did not react to the retest dose, there was a drop in sensitivity during the interval between the primary reaction and retesting. Third, diagnostic errors in primary reactions undoubtedly comprised a certain number of those who did not react a second time.

By sulfadiazine sensitivity we mean the innate or acquired ability of a person to react untowardly to sulfadiazine. In this program dermal reactions are taken as an indication of sensitivity. The manner in which these dermal reactions appeared can be divided into three classes: Into the first and largest class can be put those men who developed a rash only after having taken prophylactic sulfadiazine continuously for 5 or more days. Into the second class can be put those men who have taken their sulfadiazine interruptedly, with periods of from 4 to 28 days during which no drug was taken. This class is smaller in size than the first, but it is important from the standpoint of mass sensitization. In the third and smallest class are 22 men who developed a rash within a few hours after they took the initial dose of prophylactic sulfadiazine. Most of these men gave no history of previous contact with sulfonamides. These men may be considered to be innately sensitive or to have acquired

a sensitivity to sulfadiazine in an unknown manner. This class can be dismissed with the statement that it is unlikely that they acquired their sensitivity from our program.

Class 1.—Of the reactions observed in the Green Bay area between 1 December 1943 and 15 April 1944, 554 of the 597 have been placed in the first class. All patients had been taking sulfadiazine for at least 5 days before they developed a rash. Of this group 136 when retested developed a secondary rash. If permanent sensitivity to sulfadiazine is assumed in this class, then 1.5 men per thousand have been prevented from further use of sulfadiazine.

Of the first class 208 when retested did not react with a secondary rash, and were returned to the prophylactic program without recurrence of dermal reactions. It may be assumed that these men had not been permanently sensitized to sulfadiazine in prophylactic doses.

Of the first class 210 were not retested because of inaccessibility. If this group had a similar rate of positive reactions to retesting, then an additional 136 or 1.5 men per thousand have been prevented from further sulfadiazine therapy.

Class 2.—Four large groups of men have been under close observation during the resumption of sulfadiazine prophylaxis after varying periods of interruption.

1. In 1,400 recruits who had been taking sulfadiazine prophylaxis for 3 weeks or longer, sulfadiazine was withdrawn for 7 days. On resumption of the drug, no reactions were observed within a period of 7 days.

2. Service School, Group I, consisting of 3,580 men who had been taking sulfadiazine for 2 months with reaction rates of 1.1 men per thousand per month was withdrawn from the program during the month of February. On resumption of sulfadiazine prophylaxis in March a reaction rate of 1.9 per thousand was observed. Service School, Groups II and III, on the program in February and March gave a reaction rate of 1.5 per month.

3. From recruit camps, 27,438 men having taken sulfadiazine prophylactically longer than 1 week have been withdrawn from the program from 9 to 15 days by virtue of "boot leave." On returning from "boot leave," they were again included in the program while being held in the out-going unit. A primary reaction rate of 0.87 per thousand was observed.

4. In a group of recruit camps, sulfadiazine prophylaxis was interrupted for 4 days. On returning to the program, 21 primary reactions were observed in 24,472 men, giving a rate of 0.85 per thousand.

It must be admitted that some are sensitized to sulfadiazine by the ingestion of 1 gm. daily for 7 or more days; however, the over-all rate does not exceed the sum of the rates in classes 1 and 2 or 3.9 per thousand.

Relationship of Sulfadiazine Blood Levels, Leukocyte Counts and Immunizations to Dermal Reactions

In 300 men with primary dermal reactions, the mean blood sulfadiazine level was 1.4 mg. percent with a range of 0.0 percent to 4.2 mg. percent. This mean is not significantly different from the mean of blood sulfadiazine levels obtained on admission for respiratory disease and in well controls. Of these reactions 47 had blood levels of 0.1 mg. percent or less. It becomes apparent that the development of dermal reactions does not depend on the presence of a high sulfadiazine blood level.

One hundred cases of dermal reactions to sulfadiazine were found to have admission leukocyte counts as follows:

Normal	5,000 - 10,000	50 percent
Above normal	10,000 - or more,	41 percent
Below normal	4,000 - 5,000	6 percent
	Less than 4,000,	3 percent

All recruits within a 5-week period are immunized against typhoid, smallpox, yellow fever, and tetanus. The role of these immunizations as multiple sensitizers is unknown, but it should be pointed out that the over-all rate for dermal reactions in recruits is 4 times as great as the over-all rate in Service School personnel who received no immunizations.

Summary

1. One gram of sulfadiazine was administered daily as a prophylaxis to 188,000 enlisted personnel from December 1943 to April 1944.

2. This prophylactic measure proved highly effective in reducing the incidence of respiratory diseases.

3. Severe respiratory tract infections requiring hospitalization were reduced from 80 to 90 percent.

3. The incidence of cerebrospinal fever (meningococcic) was reduced 98 percent.

5. The incidence of streptococcal infections was reduced 85 percent.

6. The rheumatic fever rate fell strikingly. The ratio of cases occurring in areas receiving prophylaxis and control areas was 1 to 14.

7. There was also a significant but less impressive reduction in the incidence of catarrhal fever, pneumonia, otitis media, and sinusitis.

8. The incidence of mild respiratory complaints fell markedly following the institution of prophylaxis but rose to the control group level in February.

9. The ingestion of 1 gm. of sulfadiazine daily afforded a well maintained blood level of from 1 mg. to 2 mg. percent.

10. Approximately 0.39 percent of Naval personnel with this blood level developed drug reactions.

11. A few of these reactions were severe. Seven deaths occurred; however, only one of these was attributable solely to prophylaxis.

12. Further utilization of mass sulfadiazine prophylaxis is indicated, but only when initiated and supervised by experienced medical officers.

Report 4

The Streptococcal Control Program U. S. Naval Training Center, Sampson, New York

*From Epidemiology Unit 12**

In early November 1943 the Bureau of Medicine and Surgery, through the Division of Preventive Medicine, directed that a Streptococcal Control Program be inaugurated and carried on at the United States Naval Training Center, Sampson, New York. At this time, it was decided to include in this program only the recruit areas of the station, which consisted of five units, each with facilities for approximately 5,000 men. The recruits of three units were to receive 1 gm. of sulfadiazine daily per man, beginning 1 December 1943. The remaining two units were to serve as control. The administration of this program was delegated to Epidemiology Unit 12, which at that time consisted of two medical officers and five hospital corpsmen. It was later augmented by the addition of one medical officer, one bacteriologist, and two WAVES.

Administration

Edwards, Farragut, and Gilmore Units were selected as the areas to receive chemoprophylaxis. Callaghan and Dewey Units served as controls. Accurate daily records were kept of all patients with respiratory diseases seen at sick call or admitted to dispensary sickbay or the hospital or both. In addition to this, an epidemiology medical officer daily visited each recruit-unit dispensary and the hospital to confirm diagnoses

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in all cases of respiratory diseases. Throat cultures were taken of all patients with frank or probable streptococcal diseases, including scarlet fever, tonsillitis, pharyngitis, erysipelas, otitis media, mastoiditis, and sinusitis. In cases of meningococcal infection, blood cultures, nasopharyngeal cultures, and spinal fluid cultures were taken whenever possible.

Blood samples were taken for the determination of blood sulfadiazine levels from all patients with frank or probable streptococcal or meningococcal disease in the treated areas. Beta hemolytic streptococci recovered from the throat flora were isolated in pure culture, transferred to miniature blood agar slants in Kahn tubes and shipped to the Streptococcus Typing Center at the National Naval Medical Center for grouping, typing, and sulfonamide-fastness studies.

In order to establish a preliminary base line, every phase of the program, except the drug administration and culture studies, was begun on Monday, 22 November 1943. Data were collected and rounds made daily through 30 November. On 1 December every recruit in Edwards, Farragut, and Gilmore Units began to take two 0.5 gm. tablets of sulfadiazine daily at approximately 1300. The dispensing of tablets was under the direct personal supervision of each company commander and company clerk. A check-off list insured that each man received his two tablets, and he was required to swallow them with water in the presence of the company commander. No one was excused from taking the drug unless he possessed a certificate from the medical officer of his unit indicating that he was sensitive to sulfonamide.

During a 4-month period, 1 December 1943 to 1 April 1944, sulfadiazine was given prophylactically in this program to 63,392 persons; the number of days each received the drug varied from 1 day, in a small group of hypersensitive persons, to 45 days. The average daily population taking the drug varied from 12,358 in December 1943, when only three recruit areas were receiving chemoprophylaxis to 27,674 in March 1944, when the program was extended to include one additional recruit area, the Service Schools and the Ship's Company.

Laboratory Studies

Bacteriology.—Throat cultures were taken in all cases in which the diagnosis of streptococcal infection was made in both the treated and untreated groups. Cultures were plated on defibrinated horse blood agar and incubated for 24 hours. They were then examined for hemolytic streptococcus. Colonies of this organism were then picked, isolated in pure culture, and mailed to the Naval Medical School for grouping and typing. Only about 50 percent of the group A strains were typable. No type became predominant. The more common types were 5, 12 and 3. The results of the throat culture studies are summarized in tables 25 and 26.

TABLE 25.—*Streptococcus typing according to diagnosis 1 December 1943 to 28 March 1944*

Disease	Cat. fever		Tonsillitis		Pharyngitis		Scarlatina		Other R. I.		
Serologic type	C No.	P No.	C No.	P No.	C No.	P No.	C No.	P No.	C No.	P No.	Total
1			1								1
2	1				1						2
3	3	2	3	1	3						12
5	9		4		2						15
6	3		2		4						9
9	1										1
11					1						1
12	5	3	2						3		13
14	1		1		1						3
17	3	1	1		2		1				8
18			2								2
19				1	1	1					3
26	2										2
28			1								1
30	1				1						2
32	2										2
36	1										1
39			1								1
41	1			1					1		3
43					1						1
44	1										1
?	21	5	17	1	13	3	2		2	1	65
Total	55	11	35	4	30	4	3		6	1	149

C = Control (Areas C and D).
P = Areas on prophylaxis (E, F and G).

Sulfadiazine Blood Level Determinations.—A small percentage of patients taking sulfadiazine prophylaxis are known to contract streptococcal infections. One possible explanation for this is an inadequate blood level. To collect information on this point, blood levels were determined for patients who contracted streptococcal disease in the groups on the program. The results are summarized in table 27. It is seen in this table that more than half of this group had blood levels of less than 1 mg. percent. Only one of these patients had a blood level above 2 mg. percent; it is believed that otitis media in this patient was a mixed infection. The observations at this station indicated that a blood level of 2 mg. percent is desirable for protection against hemolytic streptococcal infections.

Results

Controlled Observations.—Careful clinical records of all respiratory and associated diseases were begun 10 days prior to the initiation of this program. Members of the Epidemiology Unit checked all diagnoses in the three groups on a sulfadiazine program and in the two untreated control

TABLE 26.—*Streptococcal typings according to areas*
1 December 1943 to 28 February 1944

Type	Control areas		Areas receiving prophylaxis			
	C	D	E	F	G	Total
1		1				1
2	1	1				2
3	2	7		3		12
5	9	6				15
6	4	5				9
9	1					1
11	1					1
12	5	5	2	1		13
14	3					3
17	5	2	1			8
18		2				2
19	1		1	1		3
26	2					2
28	1					1
30		2				2
32	2					2
36	1					1
39	1		1			1
41	1	1				3
43	1					1
44	1					1
?	37	18	2	5	3	65
Total	79	50	7	10	3	149

groups. Illnesses have been separated into: (1) those admitted to the dispensary sickbays for respiratory diseases; (2) those admitted to the Naval hospital for more severe respiratory diseases; (3) those admitted with streptococcal infections; and (4) those admitted with other bacterial infections.

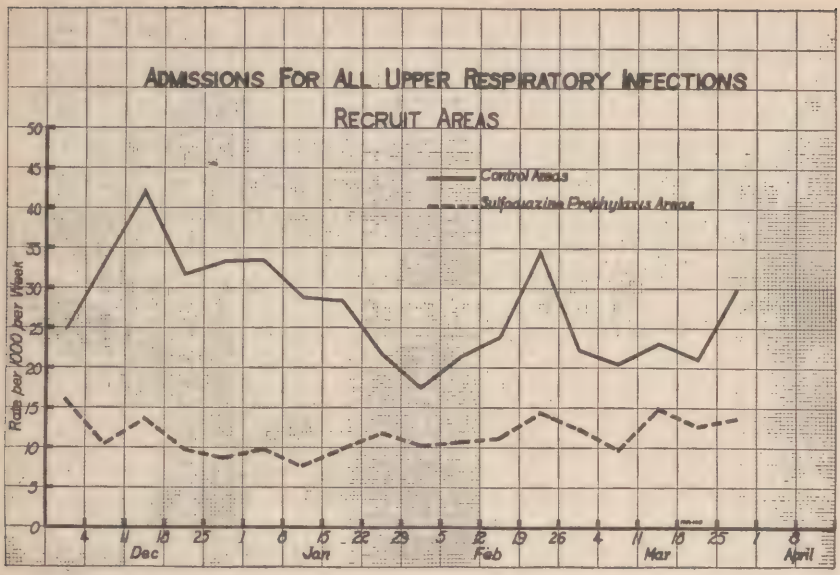
1. There is a significant difference in the rates of these diseases between the groups receiving prophylaxis and the control groups. The relative incidence of infections is shown in chart 23.

2. The difference between treated and untreated groups is even more striking in the incidence of patients admitted to the hospital. This is shown in chart 24.

3. Diseases in this category include scarlet fever; septic sore throat; tonsillitis, acute; pharyngitis, acute; otitis media, acute; and mastoiditis, acute. The significant difference between treated and untreated groups is shown in chart 25.

4. Diseases in this category include meningitis, pneumonia (lobar and bronchopneumonia), laryngitis, and sinusitis. Most of these infections are believed to be bacterial diseases other than streptococcal. The significant difference in incidence between treated and control groups is shown in chart 26.

CHART 23



Uncontrolled Observations.—In March 1944 all station personnel were placed on a daily dose of 1 gm. of sulfadiazine. Although the effect of this mass prophylaxis cannot be accurately evaluated, it was obvious to all medical and line officers that the program was highly effective. Between 15 March and 15 April a high incidence of bacterial infections of the respiratory tract was to be expected at this station; instead, the incidence of streptococcal infections was minimal. A comparison of the morbidity rates of four respiratory diseases between 1944 and 1943 is presented in table 28.

Table 28 shows that meningococcal infections were eliminated during the over-all prophylactic program; scarlet fever was reduced to a minimum; the pneumonia rate was slightly lower in 1944; catarrhal fever, which includes virus and bacterial infections, was also somewhat lower in 1944 than in 1943.

Rheumatic Fever.—One of the purposes of this program was to reduce the incidence of rheumatic fever by preventing hemolytic streptococcal nificant difference in incidence between treated and control groups is months. Only three cases of rheumatic fever occurred. All these were in the control group. In March and April 1944, when the entire station received sulfadiazine prophylaxis, there were no cases of rheumatic fever. During the same period of 1943 there were 7.5 new cases each month.

In brief, the incidence of rheumatic fever among trainees receiving sulfadiazine prophylaxis between December 1943 and April 1944 was zero. To achieve this, the incidence of streptococcal infections had to

CHART 24

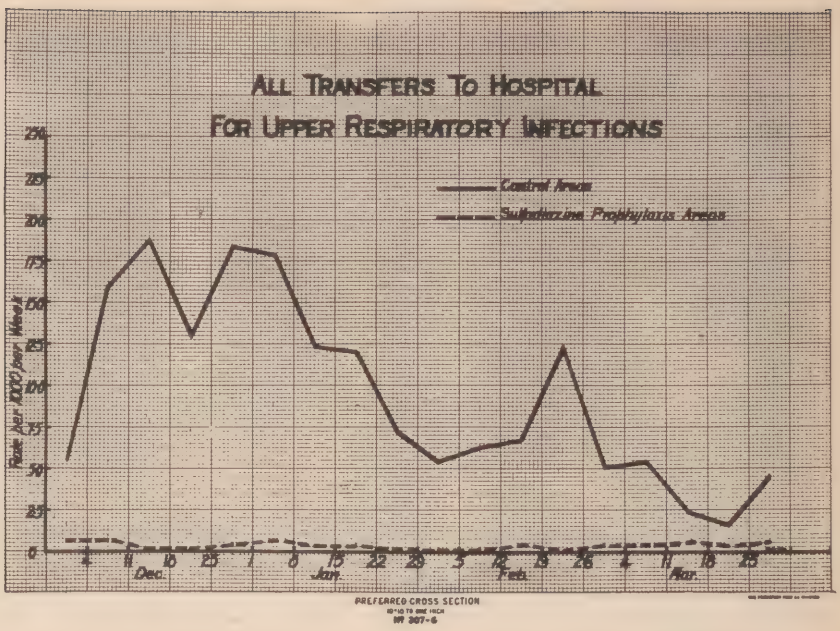


CHART 25

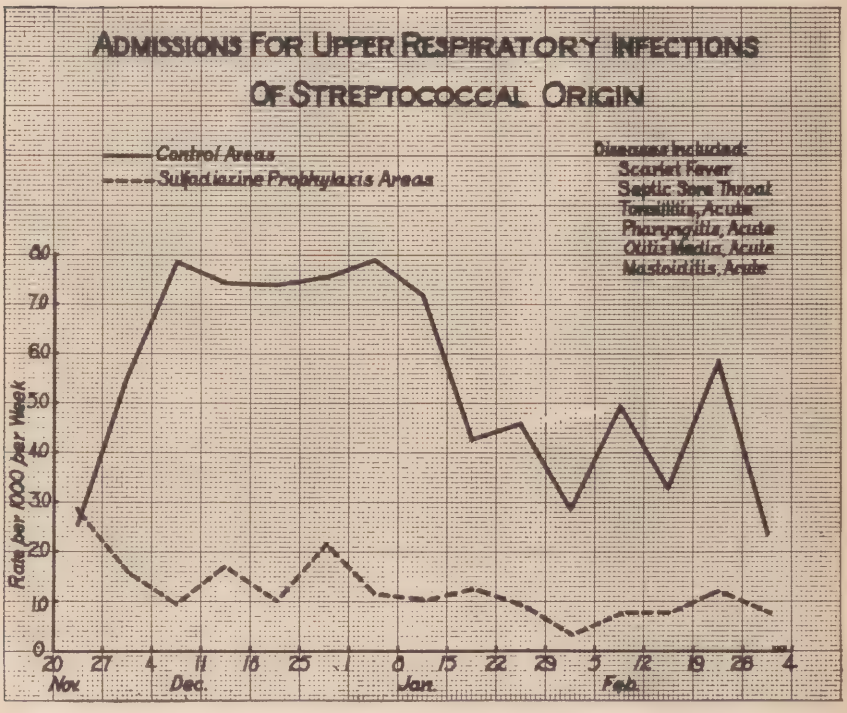


CHART 26

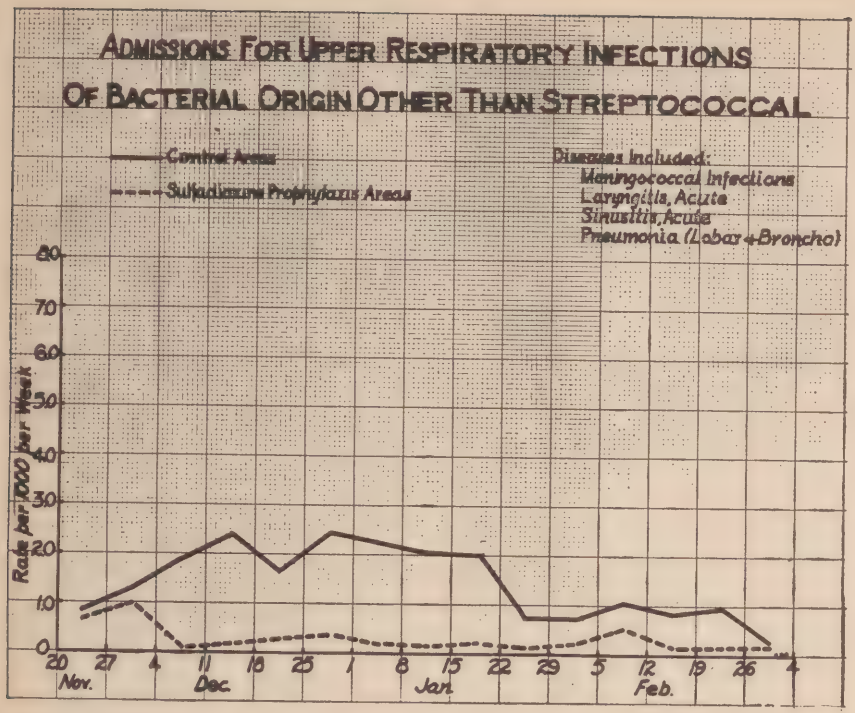


TABLE 27.—*Analysis of streptococcal disease in units receiving prophylaxis*

Unit	Date	Case no.	Duration on sulfadiazine	Type of hem. strep.	Blood sulfa level	Diagnosis
E	12/ 1/43	2	1 day	12	0.8 mg. %	Catarrhal fever.
E	12/14/43	10	13 days	12	1.8 mg. %	Do.
E	12/21/43	X	?	19	1.7 mg. %	Tonsillitis.
E	12/30/43	1	0	41	0.0	Do.
F	12/ 1/43	4	1 day	3	1.4 mg. %	Do.
F	12/ 1/43	8	1 day	19	1.7 mg. %	Pharyngitis.
F	12/ 3/43	13	3 days	3	Trace	Catarrhal fever.
F	12/ 3/43	18	3 days	?	Trace	Do.
F	12/ 6/43	8	6 days	3	Trace	Do.
F	12/30/43	5	3 days	?	1.4 mg. %	Do.
G	12/ 5/43	M-1	4 days	?	Trace	Pharyngitis.
G	12/ 6/43	10	6 days	?	Trace	Do.
G	12/30/43	6	2 days	?	Trace	Tonsillitis.
E	1 /10/44	1	21 days	?	1.5 mg. %	Pharyngitis.
E	1 /11/44	1	17 days	17	0.3 mg. %	Catarrhal fever.
E	1 /26/44	1	21 days	?	1.5 mg. %	Do.
F	1 /13/44	2	4 weeks	?	Trace	Do.
F	1 /14/44	2	7 days	12	Trace	Do.
F	1 /16/44	2	6 weeks	?	2.7 mg. %	Acute otitis media.
F	1 /17/44	2	25 days	?	Trace	Catarrhal fever.
F	1 /23/44	2	17 days	?	Trace	Do.

TABLE 28.—*Incidence of respiratory infections from 14 March 1943 to 17 April 1943 compared to a similar period in 1944*

Disease	Week ending									
	Mar. 20 1943	Mar. 18 1944	Mar. 27 1943	Mar. 25 1944	Apr. 3 1943	Apr. 1 1944	Apr. 10 1943	Apr. 8 1944	Apr. 17 1943	Apr. 15 1944
	*Rate**	*Rate**	*Rate**	*Rate**	*Rate**	*Rate**	*Rate**	*Rate**	*Rate**	*Rate**
Ctaarrhal fever, acute	1,030	707	931	738	798	726	673	617	749	683
Meningococcal infections	13.74	0.0	12.64	0.0	7.98	0.0	0.0	0.0	3.55	0.0
Pneumonia, lobar and broncho	4.58	12.5	21.07	2.80	35.9	0.0	26.6	27.4	21.3	19.1
Scarlet fever	68.6	9.9	122.2	5.61	123.7	0.0	125.4	2.95	209.7	12.7

* All rates per 100,000 per week.

be reduced to a minimum. This was accomplished by sulfadiazine prophylaxis, but only by the daily administration of the drug to all hands.

Untoward Sulfadiazine Reactions

It was anticipated that untoward reactions to sulfadiazine would occur. The majority of these were minor and evanescent. The types of reactions encountered were similar to those which occur when sulfonamides are used therapeutically. Skin eruptions comprised the majority of all drug reactions. In a few instances, involvement of the mucous membranes, blood and blood-forming organs, and the genito-urinary system was observed. The time of onset of these reactions varied. Prompt anaphylactoid reactions were seen in a few recruits who had previously experienced untoward effects from sulfonamides administered therapeutically. Most dermal reactions occurred about the fourteenth day. Reactions in those who had been taking the drug for approximately 21 days were generally of a more serious nature. No attempt was made to readminister the drug to those who developed manifestations of drug sensitivity. These men were permanently removed from the prophylactic program. Duplicate Excuse Forms were filled out by the medical officer; one copy was given to the company commander and the other placed in the files of the Epidemiology Unit for reference. Initially, intradermal sensitivity tests were made in all cases in which a dermal reaction developed. This was done to ascertain whether or not recruits exhibiting dermal reactions had a dermal sensitivity to sulfonamides. The results revealed that these persons possessed no unusual dermal sensitivity that could be demonstrated by intradermal tests with sulfadiazine.

Because no severe respiratory, streptococcal or meningococcal infections developed among the group who had been removed from the program because of drug sensitivity, we are of the opinion that prophylaxis of more than 95 percent of a total recruit period is adequate to prevent infection among those in whom chemoprophylaxis has to be discontinued.

TABLE 29.—*Analysis of drug reactions by number of days on sulfadiazine prophylaxis between December 1943 and April 1944*

Number of days on drug	Average population	Number of reactions	Rate per thousand
0–5	61,196	58	.94
6–10	56,269	417	7.41
11–15	51,453	500	9.717
16–20	46,573	198	4.251
21–25	40,678	154	3.785
26–30	33,018	84	2.544
31–35	17,180	25	1.455
36–40	5,834	8	1.374
41–45	1,859	5	2.69

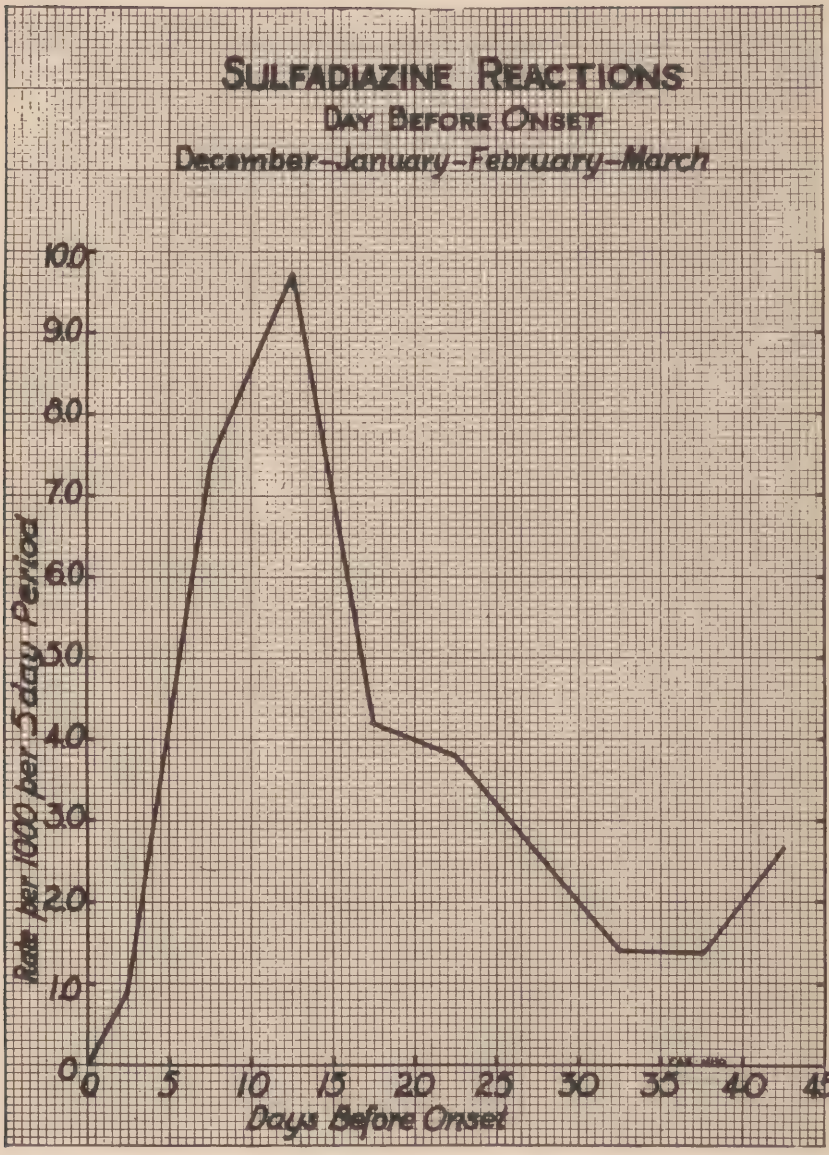
Incidence Rates.—All symptoms attributable to sulfadiazine are included in this analysis, and all these patients are classed as reactors, despite the fact that subsequent prophylactic doses may not have given rise to reactions. The over-all rate of reactions observed in this program was 2.28 percent. The incidence of reactions varied with the duration of prophylaxis. An analysis of our observations is presented in table 29, grouped in 5-day periods. It is seen in this table that the highest incidence occurs between the eleventh and fifteenth day. This is graphically presented in chart 27.

Types of Reactions.—As previously mentioned, the types of drug reactions included the following main groups: (1) dermal; (2) mucous membrane; (3) hemopoietic, and (4) genito-urinary.

Skin Reactions: Morbilliform rashes were present in more than 50 percent of cases. This rash resembled the exanthemas of rubella and rubeola to a marked degree, at times making differential diagnosis difficult. The absence of upper respiratory symptoms of a catarrhal nature, Koplik's spots and enlarged postauricular nodes was often important in establishing a diagnosis of a skin eruption due to sulfadiazine.

Scarlatiniform eruptions were the next most common form of dermal reactions observed in this series. These rashes varied from mild generalized erythemas to several degrees of punctiform eruptions. The absence of accentuation of these lesions in the flexor surfaces of the axillae, antecubital fossae and groins, and throat cultures negative for beta hemolytic streptococci helped in establishing a diagnosis in questionable cases. Urticarial lesions occurred at any stage in the course of the prophylactic program. They were most frequently observed in those recruits who gave a history of previous untoward experience with therapeutic or prophylactic doses of sulfonamides. The lesions were characterized by wheals of various sizes and shapes, usually of a dusky color. They were found to occur most frequently on the torso. Purpuric lesions were noted in a small percentage of cases. These lesions appeared on the extrem-

CHART 27


SULFADIAZINE REACTIONS
DAY BEFORE ONSET
December–January–February–March
Rate per 1000 per 5day Period
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
0
5
10
15
20
25
30
35
40
45
Days Before Onset

ities, particularly the lower extremities and soles of the feet, involving fairly large areas of the affected parts. Circinoid or annular types of lesions occurred infrequently. Exfoliative dermatitis was observed in a few persons.

Mucous Membrane: Erythema multiforme appeared in a number of instances. The lesions varied in type, size, and shape; they included macules, papules, and vesicles, frequently associated with mucous membrane lesions and fever. In a few instances, the eruption proceeded to the bullous state. These lesions varied in size, were fairly generalized, and involved mucocutaneous junctions, such as mouth, penis, and rectum. The areolae mammae were involved in a number of cases. *Free sulfadiazine was found in the fluid of these lesions several days after the last dose of sulfadiazine had been ingested.* This type of eruption was associated with lesions of the mucous membrane, such as stomatitis and conjunctivitis.

In addition, these patients exhibited generalized toxic symptoms with fever, loss of blood serum and proteins, and a tendency to an inversion of the albumin-globulin ratio. In all the severe cases and some of the moderately severe, mucous-membrane lesions occurred. Characteristically, these usually occurred in men who had taken from 18 gm. to 21 gm. of the drug. Of the mucous membrane lesions, conjunctivitis was the most frequent in occurrence. This was commonly associated with blepharitis. Conjunctivitis usually preceded more severe lesions of the erythema, multiforme complex: stomatitis, glossitis, cheilitis, exfoliative tracheobronchitis. Stomatitis and cheilitis responded slowly to treatment, and caused some difficulty in the administration of nourishment. A typical case history follows:

Report of Cases

An apprentice seaman, aged 25, white, had been on the prophylactic program for 15 days, so that he had taken a total of 15 gm. of sulfadiazine. Admitted to dispensary sickbay on 22 January 1944, complaining of a "cold" and "slight fever," the patient was put to bed and given "2 pills."

Symptoms and Diagnosis.—Shortly after admission, he broke out in a rash accompanied by pruritis which rapidly involved most of his body. On the morning of the twenty-third, he was seen by a medical officer of the epidemiology department and a diagnosis of dermatitis medicamentosa due to sulfadiazine was made. Conjunctivitis was present at this time.

Examinations of the Blood.—A sample of blood taken at this visit revealed a free sulfadiazine level of 2.0 mg. per hundred cubic centimenters of blood. The patient was transferred to the Naval hospital later in the day where another blood sample, taken approximately 12 hours later, showed a sulfadiazine level of 2.1 mg. per hundred cubic centimeters of blood.

Symptoms on Hospital Admission.—On admission to the hospital the patient was found to be acutely ill with moderate respiratory distress and slight cyanosis of the face. His temperature was 102.2° F., pulse 132, and respirations 25.

Physical Observations.—Skin: The face was dusky and reddish, and showed cyanosis with diffuse vesicular rash and small bullae on the lips at the mucocutaneous border. The neck had a vesicular type rash with large bullae on both sides. One of the blebs on the patient's neck was needled and the fluid was aspirated. The free sulfadiazine level of this fluid was 1.4 mg. per hundred cubic centimeters. Vesicular and maculopapular lesions were present on the chest. The abdomen and extremities also had dusky, red maculopapular lesions.

Eyes: Sclerae showed marked injection with dilation of small vessels. The lids showed pustular crusting, with conjunctivae injected. The pupils were equal and reacted to light and accommodation.

Mouth: A friable, grayish membrane was present over the soft palate and tonsillar fossae. There were no bleeding points. The tongue was heavily coated. There were bullae just inside the lips and on the buccal mucosa.

Ears: The ear drums were not seen. The external canals were involved with vesicular blebs, some of which were broken and discharged a serosanguineous fluid.

Lungs: Large rhonchi were heard throughout both lungs. No rales or bronchial breathing were heard.

Abdomen: No masses were felt.

Extremities: The extremities were normal except for skin lesions.

Genitalia: Genitalia were normal.

Reflexes: Reflexes were physiologically normal.

Laboratory Findings.—The urine on admission was clear and had a specific gravity 1.015; it was negative for albumin and sugar, and showed normal sediment. The sulfadiazine level was 0.9 mg. per hundred cubic centimeters.

Blood Study.—The morning of the twenty-fourth, a complete blood study was done: The red blood count was 4,210,000; hemoglobin, 11 gm.; white blood count, 10,850; total protein 7.55 gm. per hundred cubic centimeters of serum; nonprotein nitrogen 41 mg.; blood urea nitrogen 18 mg.

Treatment and Course.—At this time the chest showed many moist rales on both sides. The patient was given 1000 cc. of 5-percent dextrose in saline solution and a transfusion of 500 cc. of citrated blood. On this day the temperature was elevated to 105.5° F., and the patient looked worse. On the twenty-fifth the total protein had dropped to 5.4 gm. per hundred cubic centimeters; nonprotein nitrogen was 30, and urea nitrogen, 15. Penicillin was instituted at this time, 20,000 units were given every 4 hours, and the diagnosis was changed to bronchopneumonia. On the twenty-seventh the general condition was about the same; total proteins were 6.25; albumin was 3.95, and globulin 2.30. Another transfusion was given of 500 cc. of citrated blood, and periodic aspiration of mouth and pharnyx with a suction apparatus was begun. Because of his increased respiratory difficulty the patient was placed in an oxygen tent. On the twenty-ninth the total protein was down to 5.62 gm., albumin, 2.62, and globulin, 3.00. Nonprotein nitrogen was 29 mg. per hundred cubic centimeters.

The patient continued to have a stormy, febrile course, the temperature ranging between 101° F. and 103° F. for 21 days. He was in the oxygen tent the greater part of this time.

On 9 February 1944 a roentgenogram of the chest was taken. The report read: "There is a widespread, disseminated, exfoliative and exudative bronchitis in both lungs, more concentrated in the right base posteriorly." Skin lesions healed slowly and the conjunctivae cleared; however, the blepharitis persisted and stringy adhesions were developed at the outer canthi of both eyes.

On 8 March 1944 a follow-up roentgenogram revealed that: "The process in the right base has improved considerably, but resolution is not complete."

On 13 March 1944 the total protein was 6.72 gm. per hundred cubic centimeters. By this time the skin lesions had all healed without scarring, but they left some slight purplish discoloration.

Effects on Blood and Blood-Forming Organs: Over a 3-month period a number of patients with mild morbilliform skin reactions were admitted to one sickbay for a diagnostic record. Blood studies were made of 72 of these patients. The average erythrocyte count was 4,475,000 with a range of 3,600,000 to 5,400,000. The average white count was 7,034 with a range from 2,100 to 13,000. Sixteen or 22.2 percent of these patients had a white count of less than 5,000, a range from 2,100 to 4.990, and an average of 4,036. These patients had been taking the drug an average of 11.4 days. One patient developed a severe neutropenia. He had received 1 gm. of sulfadiazine daily for 33 days. His history follows:

The patient was admitted to the sickbay on 10 January 1944 because of a generalized rash and pruritis. The only positive findings on examination were a generalized morbilliform eruption and slight fever. On 11 January 1944 a blood count revealed that he had a secondary anemia and marked neutropenia. The red blood count was 3,850,000; hemoglobin 10.5 gm.; the white blood count 2,800; and the differential count showed monocytes, 4 percent; lymphocytes, 80 percent; granulocytes, 14 percent; and band forms, 2 percent.

The patient was transferred to the hospital for further study and treatment. On 12 January 1944 the red blood count was 3,740,000; hemoglobin 10.5 gm. and white blood count 2,600, with a differential count of monocytes, 4 percent; lymphocytes, 85 percent; granulocytes, 9 percent; and band forms, 2 percent. A transfusion of 500 cc. of whole blood was given on this day. On 13 January 1944 blood studies revealed a red blood count of 3,880,000; hemoglobin, 11 gm., white count, 4,800; monocytes, 2 percent; lymphocytes, 84 percent; granulocytes, 13 percent; and band forms, 1 percent. On 14 January 1944 the red blood count was 4,210.000 and white count 5,900 with monocytes, 5 per cent; lymphocytes, 60 percent; granulocytes, 34 percent; and band forms, 1 percent.

Subsequent daily blood studies revealed a rapid improvement in the blood picture, and on 21 January 1944 the red, white and differential counts were normal. The eruption cleared spontaneously within a few days following admission, and the patient was entirely asymptomatic during his stay in the hospital. His response to the initial blood transfusion was so prompt that further transfusions or other treatments were not necessary.

Effects on Genito-Urinary System: Urinary complications were virtually nonexistent during the entire course of the Streptococcal Control Program. It is only mentioned in this study to emphasize the fact that persons may be given small daily doses of sulfadiazine prophylactically over a long period of time without the danger of producing renal impairment of urinary tract complications. Although no special studies were made to ascertain what effects 1 gm. of sulfadiazine daily had on the urinary excretory system of the large group treated, urinalyses were made of all who reported to the dispensaries with other toxic manifestations and of those hospitalized for various other reasons not associated with the antistreptococcal program. This afforded a means of carefully sampling

two large groups who had been receiving 1 gm. of sulfadiazine daily. In these two groups there were no cases in which there was any evidence of renal or urinary tract involvement.

Estimate of Number of Man-Days Saved by Streptococcal Control Program from 1 December 1943 to 1 March 1944

In order to ascertain the number of man-days saved by the Streptococcal Control Program, the number of sick days lost by each person admitted with a respiratory infection was obtained. This was done for a 3-month period, from 1 December 1943 to 1 March 1944, when only three recruit areas received prophylaxis and when there was a suitable control group available. The number of sick days for each person in the control and treated areas was obtained from the F card of each patient. The diseases considered were catarrhal fever, acute; pharyngitis, acute; scarlet fever; bronchitis, acute; tracheitis, acute; tracheobronchitis, acute; rhinitis, acute; sinusitis, acute; otitis media, acute; mastoiditis, acute; bronchopneumonia and lobar pneumonia; cerebrospinal fever, meningococcic; and rheumatic fever.

The only factor used was:

$$\frac{\text{Population of treated group}}{\text{Population of control group}}$$

This was employed to correct for the divergence in populations which existed between the treated and control groups. Following this correction, the number of sick days in the treated group was subtracted from the number of sick days in the control group, giving the number of man-days saved. These values were obtained and then totaled. A conservative estimate of man-days saved during the controlled program is: December: 11,382; January: 12,663; February: 7,924; total: 31,969. The extension of prophylaxis to the entire station on 1 March undoubtedly doubled the number of man-days saved during the controlled program.

Summary and Conclusions

1. Sulfadiazine (1 gm. daily) was administered prophylactically to 63,392 Naval personnel from 1 December 1943 to 1 April 1944.

2. The incidence and rates of all types of bacterial respiratory tract diseases, particularly streptococcal infections, was significantly reduced.

3. Blood levels of 2.0 mg. percent appeared satisfactory for the prevention of most streptococcal diseases.

4. Rheumatic fever and meningococcus meningitis were nonexistent in recruits receiving sulfadiazine prophylaxis.

5. Evanescent phenomena attributable to sulfonamide idiosyncrasy occurred in 2.28 percent. Several severe sulfadiazine reactions occurred, but there were no deaths. Careful observation of all recruits on a prophylactic program is essential to prevent fatal reactions.

6. Over 30,000 man-days were saved in the first 3 months of the controlled program.

7. The institution of the prophylactic sulfadiazine program marks a significant advance in the mass prevention of bacterial infections of the respiratory tract, particularly those caused by hemolytic streptococcus.

Report 5

Streptococcus Prophylaxis Program U. S. Naval Training Center, Bainbridge, Md.

*From Epidemiology Unit 67**

A program for the control of streptococcal infections by the use of prophylactic doses of sulfadiazine was instituted at Bainbridge Naval Training Center in December 1943. This program was planned so that facts on the relative effectiveness of several dosages of sulfadiazine and different ways of administration might be compared and evaluated. The following questions were posed: What protection against streptococcal infections can be expected from the ingestion of sulfadiazine, 1 gm. daily? Is the administration of the drug on alternate weeks as effective as continuous prophylaxis? Is the dosage of 0.5 gm. of sulfadiazine daily as effective as 1 gm. daily? The purpose of this report is to present the results of the Streptococcal Control Program as conducted at Bainbridge between 13 December 1943 and 2 April 1944.

Functions of Epidemiology Unit 67

The administration of this program was the responsibility of Epidemiology Unit 67 which consisted of four medical officers, five pharmacist mates and a WAVE yeoman. The program was conducted under the supervision of the Senior Medical Officer of the station. Line officers were advised regarding the administration of sulfadiazine. Respiratory illnesses were checked by clinical and bacteriologic examinations. Routine diagnostic procedures were handled in the Unit's laboratory. Throat cultures were plated on horse blood agar; colonies of hemolytic strepto-

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* Participants: MILTON J. H. GRAND, Lieutenant Commander (MC) USNR; JOHN B. STANBURY, Lieutenant Commander (MC) USNR; ERNEST W. EKERMEYER, Lieutenant (MC) USNR.

Assistants: John Emmett Peters, PhM1c; James Vincent Dattilo, PhM2c; William Robert Overs, PhM2c; Robert Samuel Stone, PhM2c; Dean Graeme Jones, PhM2c.

coccus were isolated in pure culture; these organisms were then transferred to the National Naval Medical Center for serologic grouping and typing.

Organization of Five Groups of Personnel

Five groups of enlisted men were given sulfadiazine prophylaxis: (1) The Naval Academy Preparatory School (NAPS), consisting of about 600 men; (2) Regiment 1, a Service School group of about 5,000 men; (3) Regiment 2, a "boot" camp, consisting about 3,000 Negro trainees; (4) Regiment 3, a "boot" camp of about 5,000 white trainees; (5) Regiment 4, a "boot" camp of about 5,000 white men, similar to Regiment 3.

The NAPS complement remained unchanged throughout the period of observation. The Service School personnel (Regiment 1) were at Bainbridge from 6 weeks to 4 months. Recruit training lasted from 6 to 8 weeks. New recruits were admitted to Regiments 2, 3, and 4 several times each week. These regiments were maintained at full strength and the turnover was rapid. Each of the five groups had its individual sulfadiazine dosage and schedule for administration.

Administration of Sulfadiazine Prophylaxis

Two different methods were required for the dissemination of the sulfadiazine tablets: one for the recruits and one for the Service School personnel.

Recruits (Regiments 2, 3 and 4).—All recruits entering the station passed through the same receiving unit where they were formed into companies of approximately 135 men each. While in this unit, the men were housed and messed together. After 2 or 3 days, the recruits were placed in a company and billeted in permanent barracks. The sulfadiazine tablets and muster sheets were distributed to the commanders of the companies who were instructed to check the name of each man when the tablets were taken by him. At the end of each week the company commander returned the checked-off muster sheets and a new supply of sulfadiazine was issued him with another muster sheet. The company commanders were made responsible for the administration of the drug. They were informed of the importance of prophylaxis and the necessity for the strict adherence to the regularity of administration.

Service Schools (Regiment 1).—Since all the Service Schools were divided into sections of approximately 50 men each, this unit was utilized for distributing the tablets. At the beginning of each week there was a meeting with the appointed leaders of all the sections and a muster sheet and a supply of the drug were given to them. These sheets showed the names of the men, their home states and ages, and had a place for a daily check-off of the days that they received the drug or a daily check-off of

days under training if they were not receiving medication that week. These section leaders were instructed to give each man the prescribed number of tablets at 1930 each day and to observe the actual taking of the tablets. The muster sheets containing the data were collected at the end of each week and the number of days of medication in the treated group and the number of days of men under training in the untreated group were determined.

Method of Collecting and Tabulating Data

Each of the regiments was served by two dispensaries to which an assigned medical officer of the Epidemiology Unit made daily visits. From the log book in each dispensary he was informed of all patients with respiratory symptoms. He recorded the number of new respiratory sick calls for each company under separate headings. Each man admitted to sickbay or hospital for a respiratory illness was examined by this medical officer; a throat culture was taken and a tentative diagnosis was made. These cases were followed and the diagnoses were reviewed in the light of the throat culture results and additional clinical observations. These data were collected, summarized weekly, and disease rates compiled for each company in each of the study groups.

We were particularly interested in the accurate differentiation of streptococcal infections; therefore, if a patient appeared to have tonsillitis or pharyngitis but the throat culture was negative for hemolytic streptococci, the patient was given a diagnosis of "catarrhal fever, acute" in our records. However, if the medical officer made an original diagnosis of "catarrhal fever, acute" and had a subsequent throat culture of hemolytic streptococci, the diagnosis was not changed and the patient was considered to be a carrier. The number of such cases, however, was small. An occasional patient with tonsillitis, pharyngitis, or scarlet fever was found among the treated group who, through neglect or indifference, had not taken his medication according to schedule. Any man who had failed to take sulfadiazine was eliminated from the series. Here, too, the number of such persons was small. In every instance in which a streptococcal infection occurred in a treated group the patient was questioned in detail about his adherence to his prescribed schedule of drug administration and this information was checked with the muster sheets previously turned in by the section leaders.

The incidence of streptococcal disease was calculated in two ways: One of these consisted of determining the cases of scarlet fever, tonsillitis, and pharyngitis confirmed by throat cultures. The second method consisted of classifying all cases of respiratory infection with hemolytic streptococci in the flora as probable streptococcal infections.

Results of Sulfadiazine Prophylaxis

NAPS.—The purpose of the control program in this group was to protect all hands against streptococcal infections. The group consisted of 634 men who matriculated in October 1943 and engaged in training until June 1944. All hands were given 1 gm. of sulfadiazine daily. Their state of health was observed carefully and throat culture studies were made every 3 weeks of the entire student body. The results of this control program are presented in tables 30 and 31.

Table 30 shows that all but four persons escaped frank streptococcal infections and that in all the respiratory infections except five, hemolytic streptococcus was excluded as the causative agent.

Table 31 shows that hemolytic streptococcus type 1 was carried by members of this group prior to the institution of the program; that it persisted throughout the winter months, but that its prevalence did not increase. Two men acquired type 36 in the throat flora. Type 19 was strikingly predominant at Bainbridge. It manifested extreme communicability and invasiveness, and can be classified as the epidemic type throughout the period of observation; it was, however, implanted in only two members of this group.

Regiment 2.—The purpose of the program in this group was to determine the effectiveness of a daily dosage of 0.5 gm. sulfadiazine in preventing streptococcal infections. This regiment consisted of about 3,000 Negro recruits. It was divided into two equal parts: One, designated as Group B, consisted of the odd-numbered companies. Group B received 0.5 gm. of sulfadiazine daily and Group A served as an untreated control through 3 periods (4 weeks each) of observation. The entire company was given sulfadiazine, 1 gm. daily, during a fourth period of 4 weeks. The results of this program are shown in chart 28 and tables 32 and 33.

Chart 28 indicates the effectiveness of a daily prophylactic dose of 0.5 gm. of sulfadiazine and perhaps a greater effectiveness of a daily dose of 1 gm. of sulfadiazine. The incidence of sick calls for respiratory symptoms in the untreated group was twice that of the treated group and the incidence of respiratory diseases requiring bed care in the untreated group was about 3 times that of the treated group. In both sick calls and admissions the difference in incidence between the untreated and treated groups is statistically significant.

Table 32 shows that in the untreated group the incidence of respiratory infections which were probably caused by hemolytic streptococcus was 11 times that of the treated group. The incidence of frank streptococcal diseases in the untreated group was 24 times that of the treated group.

TABLE 30.—*Incidence of respiratory infections: Naval Academy Preparatory School*

Four-week period ending	Population	Sick call		Dispensary and hospital admissions for R. I.		Respiratory admissions with positive throat cultures		Tonsillitis, pharyngitis confirmed by throat culture	
		No. of cases	Rate/1,000	No. of cases	Rate/1,000	No. of cases	Rate/1,000	No. of cases	Rate/1,000
1/9/44	467.4	66	141.2	2	4.28	0.0	0.0	0.0	0.0
2/6/44	576.2	98	170.1	7	12.15	0.0	0.0	0.0	0.0
3/5/44	541.1	84	155.2	10	18.48	2	3.68	2	3.68
4/2/44	483.8	56	115.8	7	14.47	3	6.20	2	4.13

TABLE 31.—*Serologic types of hemolytic streptococcus in throat flora of "naps"*

Type	11/18/43	12/21/43	12/29/33	1/10/44	2/1/44
1	1				2
2				1	
3	2		1		
5			1		3
6	5		1	4	1
12	1			1	2
14				2	1
17	5			2	1
18	1			1	1
19				2	2
24	1			1	3
25	1				
28	1				
29		1		1	
32	1				
33	1			1	
34	5				
36					2
41		1			
A–Not Typable	3	1	2	6	15
Total	28	3	5	22	33
Total cultures	577	344	294	400	569
Carrier rate	4.85	0.95	1.70	5.50	5.79

TABLE 34.—*Incidence of respiratory infections (probably hemolytic streptococcal) and frank streptococcal diseases in regiment 4*

4-week period ending	Population average strength	Respiratory infection with positive hemolytic streptococcus						Confirmed scarlet fever, tonsillitis and pharyngitis					
		Control		Treated				Control		Treated			
		A		B		C		A		B		C	
		No. of cases	Rate/ 1000	No. of cases	Rate/ 1000	No. of cases	Rate/ 1000	No. of cases	Rate/ 1000	No. of cases	Rate/ 1000	No. of cases	Rate/ 1000
1/9/44	A–515 B–502 C–415	13	25.2	2	3.98	2	4.8	5	9.7	1	1.99	1	2.4
2/6/44	A–1055 B–925 B–925 C–857	86	81.5	29	31.4	1	1.2	56	53.2	13	14.1	0	0.0
3/5/44	A–1220 B–986 C–1052	113	92.6	28	28.4	4	3.8	84	69.7	20	20.3	3	2.85
4/2/44	3929					8	2.0					22	0.4

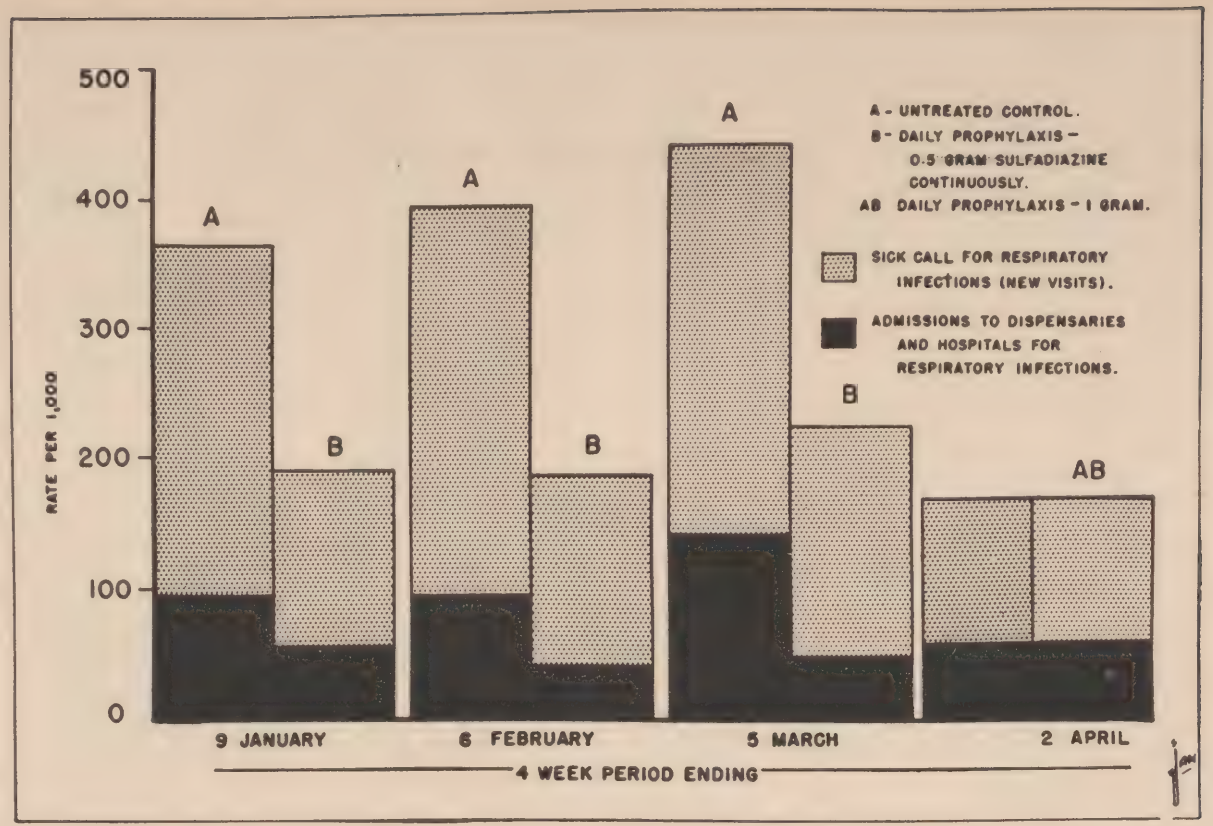
500
400
300
200
100
0
RATE PER 1,000
A
B
A
B
A
B
AB
A - UNTREATED CONTROL.
B - DAILY PROPHYLAXIS - 0.5 GRAM SULFADIAZINE CONTINUOUSLY.
AB DAILY PROPHYLAXIS - 1 GRAM.
SICK CALL FOR RESPIRATORY INFECTIONS (NEW VISITS).
ADMISSIONS TO DISPENSARIES AND HOSPITALS FOR RESPIRATORY INFECTIONS.
9 JANUARY
6 FEBRUARY
5 MARCH
2 APRIL
4 WEEK PERIOD ENDING

CHART 28

TABLE 32.—*Incidence of respiratory infections (probably hemolytic streptococcal) in regiment 2*

Four-week period ending	Population average strength		All respiratory illness with positive hemolytic streptococcus				x/σ	P
			A—control		B—treated			
	A—control	B—treated	No. of cases	Rate/1,000	No. of cases	Rate/1,000		
2/6/44	1642.2	1706.4	77	46.88	9	5.27	7.43	<0.0001
3/5/44	1430.1	1488.3	113	79.02	9	6.05	9.60	<0.0001
4/2/44	.....	2613.6	.....	.....	18	6.88	.....	.....

In summary, it appears that sulfadiazine prophylaxis, 0.5 gm. daily, reduced the incidence of respiratory diseases, reduced the incidence of respiratory infections probably caused by hemolytic streptococcus, and almost eliminated frank hemolytic streptococcal disease in these Negro recruits.

Regiment 4.—The purpose of the streptococcal control program in this regiment was to determine the comparative effectiveness of continuous prophylaxis to prophylaxis on alternate weeks. A daily dosage of 1 gm. of sulfadiazine was used. The regiment was divided into three groups by random selection. Each had an average population of about 1,500 men and this strength was maintained by the addition of new companies of recruits assigned to each group in rotation. The companies of all three groups intermingled in the barracks. Group A received no prophylaxis and served as a control; Group B received sulfadiazine, 1 gm. daily in alternate weeks; Group C received a continuous daily dose of 1 gm. The results of this program are shown in chart 29 and table 34.

TABLE 33.—*Incidence of frank streptococcal infections in regiment 2*

Four-week period ending	Population average strength		Confirmed Scarlet Fever, Tonsillitis and Pharyngitis				x/σ	P
			A—control		B—treated			
	A—control	B—treated	No. of cases	Rate/1000	No. of cases	Rate/1000		
2/6/44	1642.2	1706.4	26	15.83	2	1.17	4.56	<0.0001
3/5/44	1430.1	1488.3	64	44.75	2	1.34	7.66	<0.0001
4/2/44	.....	2613.6	.....	.....	3	1.15	.....	.....

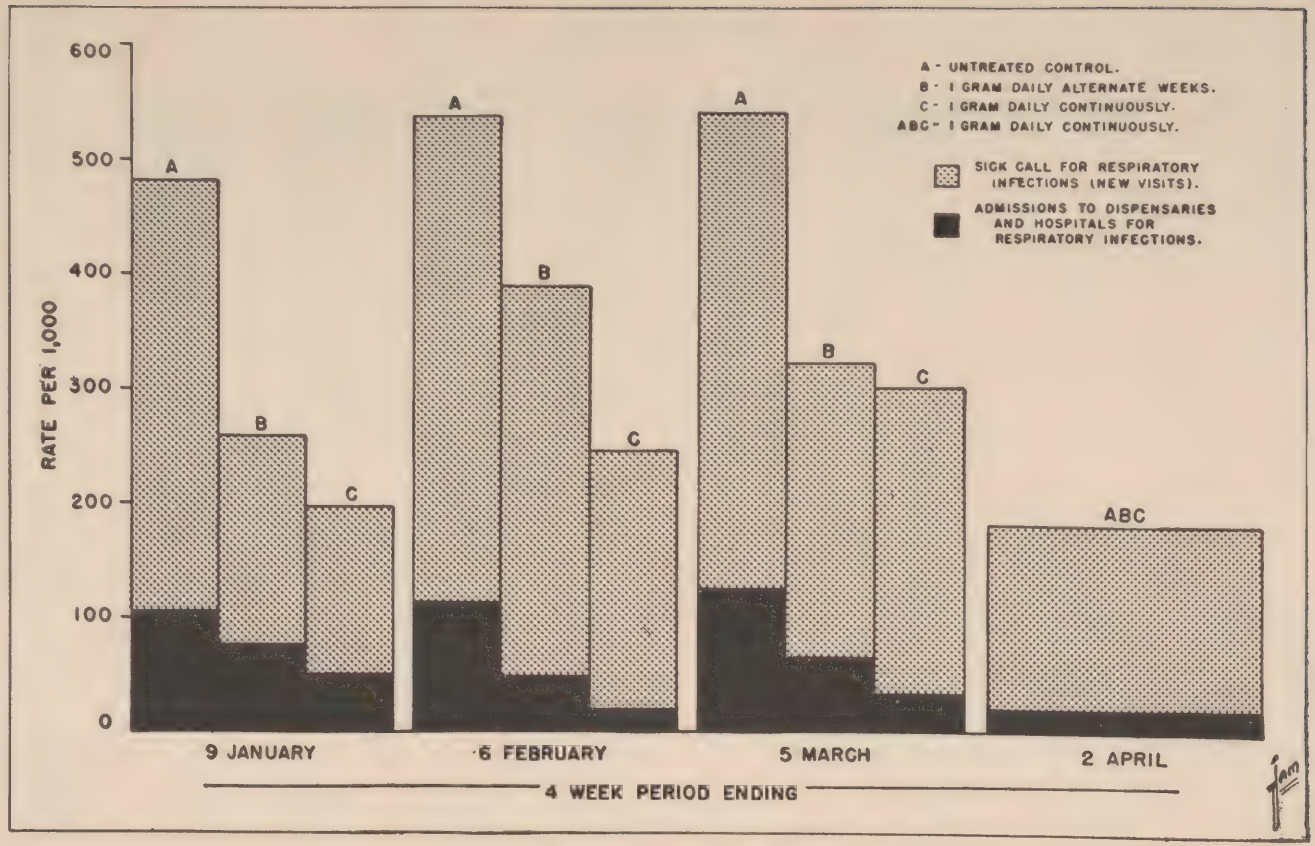
A - UNTREATED CONTROL.
B - 1 GRAM DAILY ALTERNATE WEEKS.
C - 1 GRAM DAILY CONTINUOUSLY.
ABC - 1 GRAM DAILY CONTINUOUSLY.
SICK CALL FOR RESPIRATORY INFECTIONS (NEW VISITS).
ADMISSIONS TO DISPENSARIES AND HOSPITALS FOR RESPIRATORY INFECTIONS.
RATE PER 1,000
600
500
400
300
200
100
0
A
B
C
ABC
9 JANUARY
6 FEBRUARY
5 MARCH
2 APRIL
4 WEEK PERIOD ENDING

CHART 29

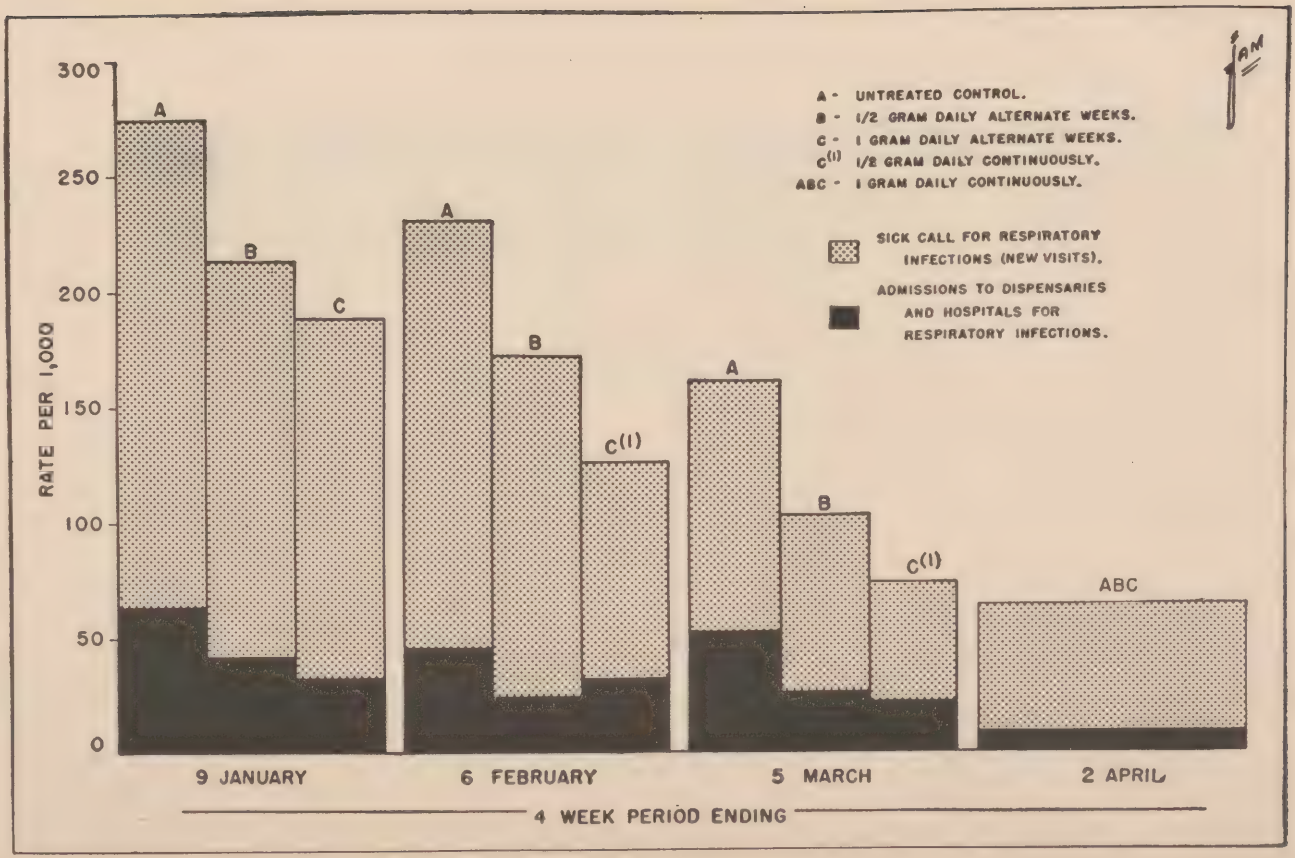
A - UNTREATED CONTROL.
B - 1/2 GRAM DAILY ALTERNATE WEEKS.
C - 1 GRAM DAILY ALTERNATE WEEKS.
C(1) 1/2 GRAM DAILY CONTINUOUSLY.
ABC - 1 GRAM DAILY CONTINUOUSLY.
SICK CALL FOR RESPIRATORY INFECTIONS (NEW VISITS).
ADMISSIONS TO DISPENSARIES AND HOSPITALS FOR RESPIRATORY INFECTIONS.
RATE PER 1,000
300
250
200
150
100
50
0
A
B
C
A
B
C(1)
A
B
C(1)
ABC
9 JANUARY
6 FEBRUARY
5 MARCH
2 APRIL
4 WEEK PERIOD ENDING

CHART 30

Chart 29 shows the relative incidence of sick calls and admissions for respiratory infections in the three groups. The sick call rate for respiratory symptoms and the admission rate for respiratory diseases show a significant difference in favor of both treated groups, but only in the second 4-week period was the continuously-treated group significantly better than the alternate-week group. The administration of sulfadiazine, 1 gm. daily, to all hands in March was accompanied by a fall in the incidence of respiratory symptoms and diseases.

Table 34 shows a striking difference between the control group and the treated groups. The group taking continuous prophylaxis had a significantly lower incidence of presumptive and proved streptococcal infections than the group receiving sulfadiazine prophylaxis in alternate weeks.

In summary, it was observed that continuous prophylaxis of 1 gm. of sulfadiazine daily was more effective; was easier to control, and caused no more untoward reactions than the administration of the drug in alternate weeks. The institution of continuous dosage of 1 gm. daily to all hands at a time when the activity of respiratory pathogens was increasing, was followed by a marked reduction in respiratory symptoms, in admissions for respiratory diseases, and especially in the incidence of streptococcal infections.

Regiment 1.—The purpose of the control program in this regiment was also to determine the relative effectiveness of continuous prophylaxis with alternate weeks of prophylaxis, using a daily dose of 0.5 gm. of sulfadiazine. This regiment, consisting of about 5,000 Service School personnel, was divided into three groups by random selection. Group A was untreated; Group B received 0.5 gm. sulfadiazine daily in alternate weeks; Group C received 0.5 gm. daily. (During the first 4-week period Group C received 1 gm. of sulfadiazine daily in alternate weeks instead of 0.5 gm. daily.) After 12 weeks the entire regiment was placed on a dose of 1 gm. administered daily. The results of this program are shown in chart 30 and table 35.

Chart 30 shows the incidence of sick calls and admissions for respiratory infections in the three groups. The difference in respiratory infection rates between the control and treated groups is statistically significant. The lowest rates occurred in the group on a program of continuous prophylaxis. The administration of sulfadiazine, 1 gm. daily, to all hands in March was accompanied by a fall in the incidence of respiratory symptoms and disease.

Table 35 shows the incidence of presumptive and frank streptococcal infections. The difference in streptococcal infection rates between the controls and groups treated with 0.5 gm. of sulfadiazine is statistically significant. The incidence of streptococcal infections in the group receiving continuous prophylaxis was slightly lower than in the group

TABLE 35.—*Incidence of respiratory infections (probably hemolytic streptococcal) and frank streptococcal diseases in regiment 1*

4-week period ending	Population average strength	Respiratory infection with positive hemolytic streptococcus						Confirmed scarlet fever, tonsillitis and pharyngitis					
		Control		Treated				Control		Treated			
		A		B		C		A		B		C	
		No. of cases	Rate/ 1000	No. of cases	Rate/ 1000	No. of Cases	Rate, 1000	No. of cases	Rate/ 1000	No. of cases	Rate/ 1000	No. of cases	Rate/ 1000
1/9/44	A–1287 B–1468 C–1393	0.0	0.0	0.0	0.0	0.0	0.0	31	24.08	15	10.22	10	7.17
2/6/44	A–1405 B–1580 C–1534	47	33.44	23	14.55	22	14.34	31	22.05	17	10.75	18	11.73
3/5/44	A–1327 B–1577 C–1551	37	27.87	21	13.32	17	10.96	30	22.60	14	8.88	10	6.44
4/2/44	4334												
4/2/44	4334					17	3.92					11	2.53

taking the drug in alternate weeks. The institution of a continuous daily dose of 1 gm. in March was followed by a striking reduction in the incidence of these infections.

In summary, it was observed that a prophylactic dose of sulfadiazine, 0.5 gm. daily, was effective; continuous dosage appeared to be preferable to the administration of the drug in alternate weeks. Increasing the daily dose of sulfadiazine from 0.5 gm. to 1 gm. on 5 March 1944 when the incidence of streptococcal infections was rising throughout the untreated groups was followed by a further marked reduction in the rate of presumptive and frank streptococcal infections.

Regiment 3.—This regiment of about 5,000 trainees received no prophylaxis until 25 February. Between 13 December 1943 and 25 February 1944 there were 95 cases of frank scarlet fever. The causative agent was serologically identified in the majority of cases as hemolytic streptococcus type 19. During February the incidence of scarlet fever rose sharply. Concomitant with this there was a sharp rise in the rate of other streptococcal respiratory infections. It was therefore believed necessary to check this sudden development by instituting a sulfadiazine program. On 25 February 1944 half of the regiment was placed on a sulfadiazine program of 1 gm. daily. The results of treating half of this regiment during a severe streptococcal outbreak are shown in charts 31 and 32.

Chart 31 shows the effect of sulfadiazine prophylaxis on the sick call and admission rates for respiratory infections. Chart 32 shows the effect of sulfadiazine on the scarlet fever rate. Except for the first week of the program, during which the treated received only three doses of sulfadiazine, there was a statistically significant difference between treated and untreated groups in the rates of respiratory infections and scarlet fever.

Serologic Types of Hemolytic Streptococcus Prevalent at Bainbridge

All strains of hemolytic streptococcus recovered from those on the prophylactic program and appropriate samples of strains from infected persons in the control groups were shipped to the National Naval Medical Center for typing. The types recovered from patients with respiratory infections are presented in tables 36 and 37. Type 19 was the prevalent type at Bainbridge throughout this period of observation.

Untoward Reactions

More than 36,000 men received sulfadiazine prophylaxis during this 4-month period. The duration of prophylaxis varied from 4 weeks in recruits to 4 months in the "NAPS." Altogether 85 men developed symptoms referable to sulfadiazine. These were classified as follows: Urticarial rash, 27; morbilliform rash, 20; scarlatiniform rash, 18; other

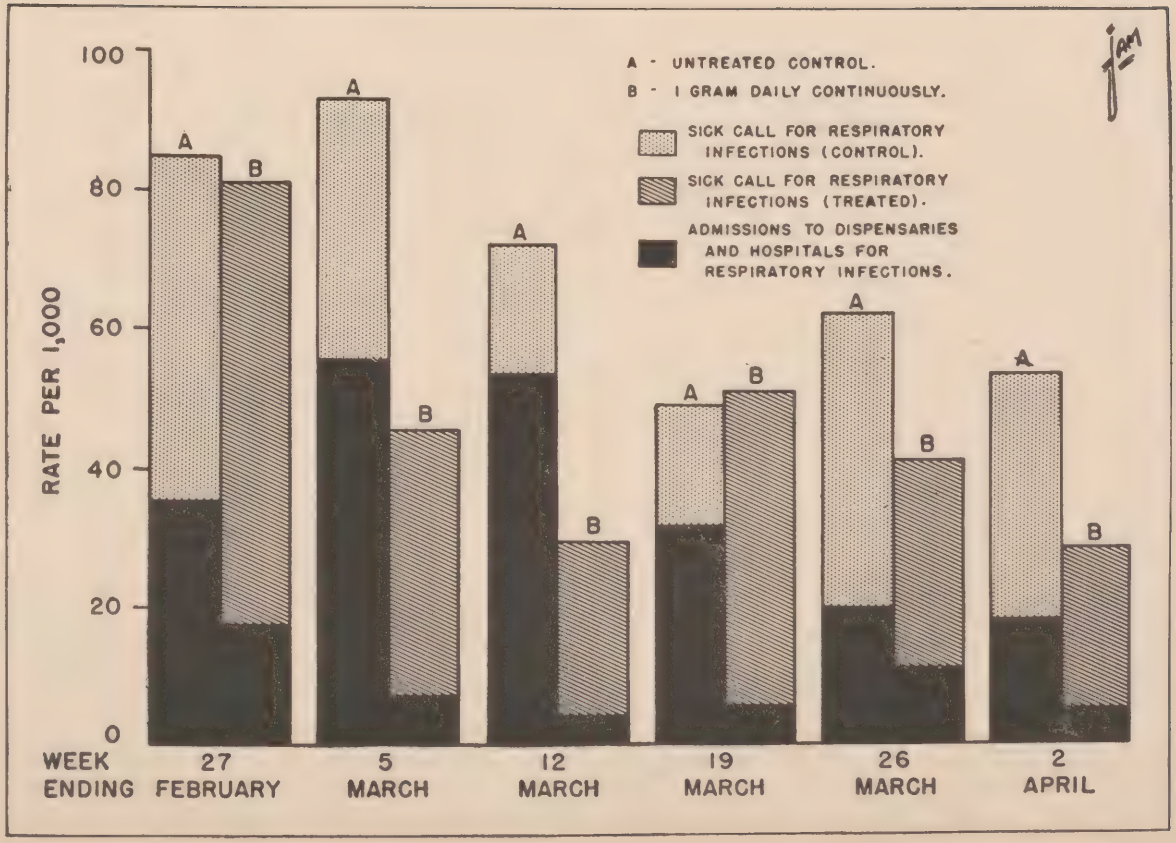
A - UNTREATED CONTROL.
B - 1 GRAM DAILY CONTINUOUSLY.
SICK CALL FOR RESPIRATORY INFECTIONS (CONTROL).
SICK CALL FOR RESPIRATORY INFECTIONS (TREATED).
ADMISSIONS TO DISPENSARIES AND HOSPITALS FOR RESPIRATORY INFECTIONS.
RATE PER 1,000
100
80
60
40
20
0
WEEK ENDING
27 FEBRUARY
5 MARCH
12 MARCH
19 MARCH
26 MARCH
2 APRIL

CHART 31

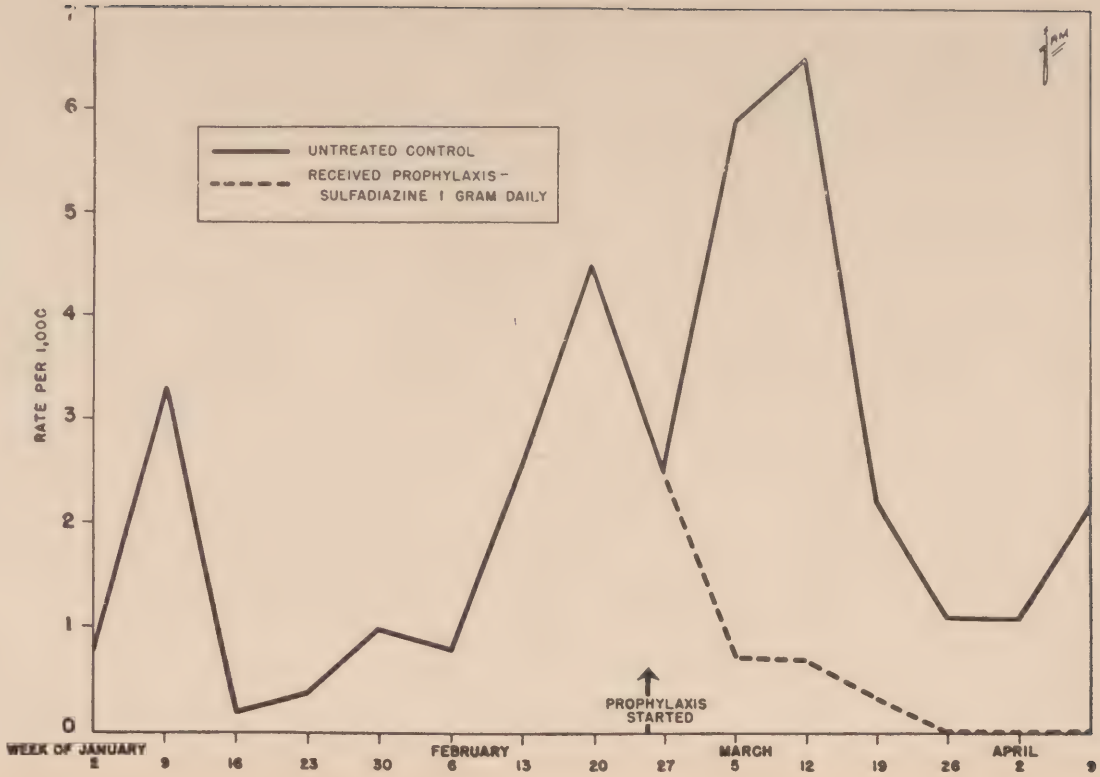
UNTREATED CONTROL
RECEIVED PROPHYLAXIS - SULFADIAZINE 1 GRAM DAILY
RATE PER 1,000
0
1
2
3
4
5
6
7
PROPHYLAXIS STARTED
WEEK OF JANUARY
2
9
16
23
30
FEBRUARY
6
13
20
27
MARCH
5
12
19
26
APRIL
2
9

CHART 32

TABLE 36.—*Incidence of serologic types of hemolytic streptococcus in various respiratory infections*

Serologic Type:—	1	2	3	4	5	6	7	12	13	14	17	18	19	24	28	29	30	41	43	44	A–NT
Catarrhal fever, acute	6	1	3		4	5		2			5	20	81	7		1	4			1	26
Scarlet fever					1			1			2	1	2				2				
Tonsillitis, acute	13	1	8		6	5		4		1	4	20	100	9			12		1		23
Pharyngitis, acute	9		4	1	1	1	2	2	1		4	14	61	5	1		2	1	1		19
Laryngitis, acute													2								
Bronchitis, acute													5								
Tracheobronchitis					1						1	4	2	1					1		1
Sinusitis, acute			1			1					4	2	6	1							
Otitis media, acute					1						1	2	9								1
Pneumonia, broncho								1					2			1					
Pneumonia, lobar						1					1	1	2								
Rheumatic fever and nephritis								1				1	1								3
Other respiratory												1	2								1
Other diseases												3	3								1
Total	28	2	16	1	14	13	2	11	1	1	22	69	278	23	1	2	20	1	3	1	75

TABLE 37.—*Serologic types of hemolytic streptococcus in different regiments*

Type	Regiment Number 1 period ending			Regiment Number 2 period ending			Regiment Number 4 period ending			"NAPS" period ending				
	1/9/44	2/6/44	3/5/44	1/9/44	2/6/44	3/5/44	1/9/44	2/6/44	3/5/44	12/21/43	12/29/43	1/10/44	2/1/44	2/18/44
1	3	7	5	1	3	1		6	2			1	2	1
2	1		1											
3		6	2				4	4			1			2
4				1										
5	2	10						2			1		3	
6	1			1	8	1			2		1	4	1	5
7								2						
12	3			1		1		2	4			1	2	1
13			1											
14			1									2	1	
17		4	2			10		2	4			2	1	5
18	12	18	4	1	2	4	8	14	5			1	1	1
19	5	29	7	12	53	58	9	77	26			2	2	
24	4	4			3		1	10	1			1	3	1
28														1
29						1	1	1		1		1		1
30	7	8	2					3						
32														1
33												1		1
34														5
36													2	
41							1			1				
43							1	1						
44						1	1							
Group A not typable	2	20	5	1	9	7	5	15	11	1	2	6	15	3

dermal lesions, 12; exfoliative dermatitis, 3; stomatitis, 4; questionable circulatory collapse, 1. Of these 28 were retested and 19 of the 28 were able to resume the drug. The relation of drug reaction to dosage is shown in table 38 and 39. It is seen that the schedule of drug administration had little effect on the rate of dermal reactions. Untoward symptoms in most developed in the second or third week when from 7 gm. to 20 gm. of the drug had been ingested. Five patients developed reactions during the first days of prophylaxis.

There were altogether five severe dermal reactions. Two patients became critically ill. There was one death which proved at autopsy to be associated with leukemia.

Report of Cases

Case 1.—A second class seaman, aged 25, was admitted to the station dispensary because of a rash, vomiting, and blisters in his mouth. He had been taking 0.5 gm. of sulfadiazine daily for 2 weeks. He gave a history of sensitivity to wool. He had recently arrived from his "boot" training elsewhere where several cases of bullous stomatitis had occurred.

Examination on entry showed a temperature of 102° F.; edema of the face and hands; a few blister-like lesions in the mouth, measuring about 4 mm. in diameter, and a discrete macular, erythematous rash on the chest, abdomen, and extremities. Fine vesicles were seen in the centers of some of these lesions.

Urinalysis on admission was normal and showed a few sulfonamide crystals in the sediment.

The red blood count was 4.84 million with 92 per cent hemoglobin; the white count was 20,050 with 75 percent neutrophils.

For the next 10 days the patient's temperature was elevated to 102° F. The oral lesions sloughed, ulcerated, and made eating and drinking extremely difficult. The cutaneous lesions rapidly subsided. On the twenty-second hospital day the patient developed right lobar pneumonia which was treated with 250,000 Oxford units of penicillin. The patient was discharged essentially well on the forty-second hospital day.

Case 2.—An 18-year old colored steward's mate was admitted to the dispensary and transferred to the hospital because of a rash and symptoms of a respiratory infection. He had been receiving prophylactic sulfadiazine, 1 gm. daily, for 14 days. A diagnosis of German measles was made. On arrival at the hospital, signs suggestive of pneumonia were found, but his general condition became progressively worse. He developed a brawny edema of the face, chest, and arms, and some scaling of the skin. Clinical evidence of pulmonary disease increased through the course of his illness. His temperature ranged from 101° F. to 104° F. Blood and urine showed no noteworthy abnormalities. Throat culture was negative for hemolytic streptococci and two blood cultures were negative.

Treatment and Course: The patient was treated with large doses of penicillin for pneumonia. He was placed in an oxygen tent on the tenth day, but this did not improve his condition and he died on the eleventh day.

Autopsy: Postmortem examination revealed gross evidence of bilateral bronchopneumonia, a liver weighing just over 2,000 gm. which, on cut surface, was somewhat pale. The spleen weighed slightly over 600 gm., was deeply colored, friable, and showed several healed infarcts. The right kidney showed

TABLE 38.—*Sulfonamide reactions in relation to drug schedule*

Method of administration	0.5 gm. alternate weeks	0.5 gm. continuously	1 gm. alternate weeks	gm. continuously
Number of men	4,470	4,414	6,160	21,051
Rate per 1,000 of dermal reactions	3.57	2.26	2.92	4.18

TABLE 39.—*Sulfonamide reactions in relation to total drug ingested*

Grams of sulfadiazine	Number cases	Grams of sulfadiazine	Number cases
1	5	11–15	42
2	3	16–20	27
3	1	21–25	13
4	1	21–25	8
5	0	Over 30	5
6–10	27		

evidence of an old healed pyelonephritis. There was a megalo-ureter on that side. The other kidney was slightly larger than normal. There was generalized lymphadenopathy. On microscopic examination this proved to be leukemia.

Comparative Prophylactic Effects of 1 Gm. and 0.5 Gm. of Sulfadiazine Administered Daily

The relative effectiveness of these two doses was tested in Regiments 1 and 2. In each of these regiments the group receiving a daily dose of 0.5 gm. of sulfadiazine in February was given a 1 gm. dose in March. In Regiment 2 with a low rate of respiratory disease the increased dosage had little or no effect. In Regiment 1 with a moderate rate of respiratory infections there was a striking improvement following the increase in dosage from 0.5 gm. to 1 gm. The sick calls rate fell from 73 to 63; the hospital admission rate from 22 to 7; the incidence of probable streptococcal infections from 11 to 4; the incidence of frank streptococcal infections from 6 to 2. These changes occurred during March at a time when the incidence of streptococcal disease was rising in the untreated group of personnel. It appeared that a daily dose of 1 gm. of sulfadiazine was more effective than 0.5 gm. in Regiment 1.

Comments

1. Will sulfadiazine prophylaxis create drug-fast strains of hemolytic streptococcus? The clinical observations made at Bainbridge suggest that none of the sulfadiazine schedules in this prophylactic program created drug-fast strains.

2. Will sensitization result from the use of alternate weeks of prophylaxis? A small percentage manifested a drug idiosyncrasy; however, prophylaxis did not appear to sensitize these recruits.

3. If the institution of prophylaxis prevents respiratory infections, will this affect the respiratory rate in the untreated companies of the regiment? It was observed that the untreated companies of the regiments engaged in the prophylactic program escaped a severe streptococcal outbreak, such as occurred in the untreated regiment. Whether this was due to a reduction in the number of susceptibles in the regiment is unkown.

Summary

1. Sulfadiazine prophylaxis was administered to five regiments at the Bainbridge Naval Training Center.

2. Several drug dosages and schedules were tested to determine the most effective and simplest standard for mass prophylaxis.

3. Continuous daily dose of 0.5 gm. of sulfadiazine was found simple to administer and effective in preventing respiratory diseases.

4. The rates of bacterial infections of the respiratory tract in recruits receiving this dosage were significantly less than in the untreated controls.

5. The institution of a station-wide sulfadiazine prophylactic program of 1 gm. daily on 1 March 1944 was followed by a striking drop in respiratory disease rates.

6. It appeared that a daily sulfadiazine dose of 1 gm. was somewhat more effective than 0.5 gm.

7. A daily dose of 1 gm. sulfadiazine appeared highly effective in: (a) checking a scarlet fever outbreak; (b) significantly reducing the incidence of streptococcal infections throughout the station; and (c) preventing the implantation of hemolytic streptococcus in the throat flora of 600 men attending the Naval Academy Preparatory School throughout the winter and spring months.

Report 6

The Streptococcal Control Program U. S. Naval Construction Center, Davisville, R. I.

*From Epidemiology Unit 42**

Sulfadiazine prophylaxis was instituted at the U. S. Naval Construction Center, Davisville, Rhode Island on 15 November 1943. The objectives of the program were to control streptococcal infections, determine the effectiveness of sulfadiazine prophylaxis, and assess the relative value of several doses and schedules of administration. The present report is a summary of our observations made between November 1943 and March 1944.

Administration of Sulfadiazine

Alternate battalions were designated on arrival on the station either as a treated or a control group. The method found most satisfactory for the dispensing of tablets was to have the company commander (Chief Petty Officer) obtain a supply of tablets from the battalion sickbay and dispense the tablets at morning muster, using a check-off list.

The chiefs were instructed to witness the ingestion of the drug; nevertheless, a certain number failed to swallow the drug. In order to obtain the cooperation of the men, various methods were used to explain the purpose of the study. The battalion medical officer spoke to the men as a group, stressed the prophylactic value of the drug, and explained the possibility of reactions. The station paper *(Bulldozer)* published articles explaining the purpose, and later, published the results of the study. Suitable posters in cartoon form were posted on bulletin boards, and the medical officer of the unit spoke to the hospital corpsmen regarding prophy-

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* Participants: W. A. Myers, Lieutenant Commander (MC) USNR; W. T. Kees, Lieutenant Commander (MC) USNR; Theodore Cohn, Lieutenant, (jg) H-V(S), USNR; W. E. Mosher, Jr., Lieutenant (MC) USNR; J. L. Garey, Lieutenant (MC) USNR.

laxis. The lifting of liberty cards of men who did not take their tablets was found to be a fairly effective method of checking delinquency in taking the drug.

Several different methods of administration and dosages were used:

SULFADIAZINE TREATED GROUPS

	Dose	*Administration*
A.	1 gm.	Daily
B.	1 gm.	Every other day
C.	1 gm.	Twice weekly
D.	0.5 gm.	Daily

Schedules other than daily proved unsatisfactory because of administrative difficulties, and they were therefore discontinued.

Clinical Results

This report can best be presented by dividing the observations into three periods: (1) 15 November 1943 to 1 January 1944; (2) 1 January 1944 to 1 March 1944, and (3) 1 March 1944 to 1 April 1944.

First Period of Prophylaxis.—An epidemic of influenza was experienced during late November and December. At this time the incidence of carriers of hemolytic streptococcus was low and this organism failed to become active. The data collected in December are presented in table 40. The rates for sick calls and dispensary admissions were comparable in the three treated groups and were lower than in the control group.

Second Period of Prophylaxis.—The data for January are presented in table 41. It is seen in this table that the incidence of disease in each of the treated groups was lower than in the control group. The group receiving sulfadiazine, 1 gm. daily, had the lowest incidence of infections. The data for February are presented in table 42. It is seen in this table that the treated battalions had a lower incidence of disease than the controls and that a daily dose of 1 gm. of sulfadiazine appeared more effective than a similar dose given every second day. In the station forces a daily dose of 0.5 gm. appeared to lower the incidence of admission.

Third Period of Prophylaxis.—On 1 March 1944 all station personnel were placed on a daily dose of 1 gm. of sulfadiazine. The control group was thereby abandoned. Efforts were concentrated on more careful clinical and bacteriologic studies of patients who developed disease while receiving prophylaxis. Sample questioning was conducted to determine what percentage of men failed to take sulfadiazine and this number was found to be about 10 percent. A striking diminution of bacterial respiratory diseases occurred in March 1944.

TABLE 40.—*Statistical summary for month of December 1943**

Average daily population	2136		985		941		3882	
Dosage schedule	1 gram daily		1 gram every 2 days		1 gram 2 times per week		Control	
Diagnoses	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Sick call U. R. I. complaints	2,008	743.8	689	648.7	700	743.8	4.249	1102.5
Dispensary admissions U. R. I.	45	21.06	12	12.1	15	14.9	129	33.4
All R. I.	45	21.06	12	12.1	15	14.9	135	34.9
Scarlet fever	0	0.0	0	0.0	0	0.0	0	0.0
Tonsillitis and pharyngitis	4	1.9	0	0.0	0	0.0	11	2.8
Pneumonia, lobar	0	0.0	0	0.0	0	0.0	4	1.0
Pneumonia, virus	0	0.0	0	0.0	0	0.0	0	0.0
Cerebrospinal fever	0	0.0	0	0.0	0	0.0	1	0.72
Gonorrhea	0	0.0	0	0.0	0	0.0	9	2.3
Drug reactions	2	0.93	0	0.0	0	0.0		

* Rate is cases per 1,000 per month. U. R. I. is upper respiratory infection. R. I. is respiratory infection.

TABLE 41.—*Statistical summary for month of January, 1944*

Average daily population	1897		466		523		721		3072	
Dosage schedule	1 gram daily		1 gram every 2 days		1 gram 2 x per week		Batt.* & S. F. 0.5 gram daily		Control	
Diagnoses	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Sick call U. R. I. complaints	714	376.3	271	581.5	255	487.5	233	323.1	1,512	492 1
Dispensary admissions U. R. I.	4	2.1	1	2.1	3	5.7	3	4.2	49	15.9
All R. I.	4	2.1	1	2.1	3	5.7	3	4.2	50	16.1
Scarlet fever	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Tonsillitis and Pharyngitis	0	0.0	0	0.0	1	2.0	1	1.4	8	2 6
Pneumonia, lobar	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3
Pneumonia, virus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cerebrospinal, fever	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Gonorrhea	0	0.0	1	2.1	0	0.0	0	0.0	6	1.9
Drug reactions	2	1.0	0	0.0	1	2.0	2	2.8	0	0.0

* Batt. is Battalion and S. F. is Station Force.

TABLE 42.—*Statistical summary for month of February, 1944*

Average daily population	2711		2381		2467		1509		2116	
Dosage schedule	1 gm. daily		1 gm. every 2 days		Control		0.5 gm. daily S. F.*		Control	
Diagnoses	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Sick call U. R. I. complaints	901	332.3	958	402.3	702	284.5	153	101.4	234	110.6
Dispensary admissions U. R. I.	5	1.8	9	3.8	27	10.9	12	7.9	44	20.8
All R. I.	5	1.8	9	3.8	30	12.2	15	9.9	46	21.7
Scarlet fever	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Tonsillitis and Pharyngitis	0	0.0	0	0.0	6	2.4	0	0.0	4	1.9
Pneumonia, lobar	0	0.0	0	0.0	3	1.2	0	0.0	2	1.0
Pneumonia, virus	0	0.0	0	0.0	1	0.4	0	0.0	0	0.0
Cerebrospinal, fever	0	0.0	0	0.0	1	0.4	0	0.0	0	0.0
Gonorrhea	0	0.0	2	0.8	5	2.0	4	2.6	2	1.0
Drug reactions	2	0.7	1	0.4	0	0.0	6	4.0	0	0.0

* S. F. is station force.

Observations on Sulfadiazine Reactions

Untoward reactions to sulfonamide were observed in a small percentage of cases. This varied in different groups between 1 and 4 per thousand. Most of the reactions were mild. The drug was discontinued for 10 days in those with untoward symptoms and then most of the men were retested to determine whether they were truly sensitive to sulfonamide. There were no serious or fatal reactions; one patient had an ulcerative stomatitis and bullous erythema on his hands.

Observations on Gonorrheal Urethritis

All patients taking sulfadiazine for 48 hours prior to exposure were considered to be in the treated group. Those who ingested sulfadiazine after exposure and those who received no sulfadiazine were placed in the control groups: 81 infections occurred; 8 of these were in the treated group and 73 in the control. The rates per thousand were 0.8 per thousand per month in the treated groups and 5.0 per thousand per month in the controls. Only 2 cases occurred in men taking a daily dose of 1 gm. The administration of 0.5 gm. daily as prophylaxis was ineffective. Some men who failed to have prophylaxis prior to exposure took 1 gm. of sulfadiazine 24 hours later. This was also found to be ineffective.

Laboratory Studies

Two laboratory studies were made: bacteriologic examinations of the throat flora, and determinations of the sulfadiazine blood level.

1. Throat cultures were studied of all patients with respiratory infections. Standard technics were used for recovering and isolating hemolytic streptococcus in pure culture. Strains of this organism were shipped on blood agar slants to the National Naval Medical School for grouping and typing, and the results were returned to the station laboratory. None of the patients who contracted respiratory infections while on the sulfadiazine prophylaxis program had group A hemolytic streptococcus in the throat flora. Group A strains were recovered from the untreated group with respiratory infections and were found to include many types: 14, 36, 18, 30, 19, 6, and 1. No type showed any tendency to spread through this station during the winter and spring months of 1944.

2. The sulfadiazine content of the blood was examined to determine: (a) whether sick personnel had lower blood levels than well personnel; (b) whether the blood level reflected the prophylactic dose ingested; (c) whether an effective blood level is maintained for hours or days after the drug is discontinued; (d) whether persons developing sulfonamide reactions have unusual blood levels or unusual proportions of conjugated sulfonamide. The results are expressed in milligrams percent and presented in tables 43, 44, and 45.

TABLE 43.—*Sulfadiazine blood levels in cases admitted to dispensary*

Dose	High	Median	Low	Total cases
1 gram daily	4.9	2.2	Trace	57
0.5 gram daily	1.7	1.2	Trace	24

Sulfadiazine blood level in well personnel

Dose	High	Median	Low	Total cases
1 gram daily	2.6	2.2	1.7	4
0.5 gram daily	1.8	1.4	0.8	1

TABLE 44.—*Fall in blood sulfadiazine level on stopping prophylaxis of 1 grain daily*

Hours after discontinuance	High	Median	Low	Number of cases
36	1.6	0.6	Trace	12
48	1.0	0.8	0.6	9
60	1.7	0.6	Negative	4
72	0.8	0.5	Negative	5
96	0.4	0.2	Trace	4
108	0.6	0.6	0.6	1
120	0.5	0.2	Negative	3
136	Trace	Trace	Trace	1

TABLE 45.—*Variations in free and conjugated sulfadiazine blood levels**

Cases	Total level	Free level	Conjugated	Percent Conjugation
1	1.9	1.7	0.3	13.66
2	4.9	4.1	0.9	17.80
3	2.1	1.7	0.5	21.17
4	1.6	1.1	0.5	28.64
5	1.0	0.5	0.6	55.76
6	2.1	2.0	0.1	6.62
7	2.3	1.6	0.7	30.30
8	3.2	2.3	0.8	24.16
9	2.7	2.3	0.4	16.37
10	2.7	2.1	0.6	23.36

* All blood levels expressed as mg. %.

TABLE 46.—*Comparison of rates of contagious diseases during January and February 1944 with January and February 1943*

Average daily population	5104		7019		12538	
	1944 treated group		1944 untreated group		1943 untreated	
Diseases	Cases	Rate *	Cases	Rate *	Cases	Rate *
Cerebrospinal fever (meningococcic)	0	0	4	0.28	69	02.8
Catarrhal fever, acute	29	2.8	191	13.6	1.926	76.8
U. R. I.	37	3.6	243	17.3	2.022	80.6
Pneumonia, lobar, broncho	1	0.09	12	0.8	13	0.05
Pneumonia, virus	0	0	1	0.05	3	0.01
Scarlet fever	0	0	0	0	3	0.01
All respiratory disease	41	4.0	256	18.1	2,104	83.9
Gonorrhea	6	0.7	45	3.2	14	0.05
Infectious jaundice	3	0.3	9	0.6	0	0
Measles	7	0.7	9	0.6	24	0.95
Measles, German	16	1.5	5	0.3	186	7.4
Mumps	9	0.9	23	1.6	23	9.1
Rheumatic fever	0	0	5	0.35	3	0.01

*Note: Rate per 1,000 per month.

TABLE 47.—*Statistical summary for months of January and February 1944*

Average daily population	2,305		1,423		1,1115		3,827	
Dosage Schedule	1 gram daily battalion		1 gram every 2 days battalion		0.5 gram daily		Control battalion	
Diagnoses	No.	Rate	No.	Rate	No.	Rate	No.	Rate
U. R. I.	9	1.9	10	3.5	15	6.70	120	15.7
All R. I.	9	1.9	10	3.5	18	8.07	126	16.5
Scarlet fever	0	0	0	0	0	0	0	0
Tonsillitis and pharyngitis	0	0	0	0	1	0.9	18	2.3
Pneumonia, lobar	0	0	0	0	0	0	6	0.73
Cerebrospinal fever (meningococcus)	0	0	0	0	0	0	1	0.13
Gonorrhea	0	0	2	0.7	4	1.8	13	1.7
Drug reaction	4	0.1	1	0.3	10	4.5		

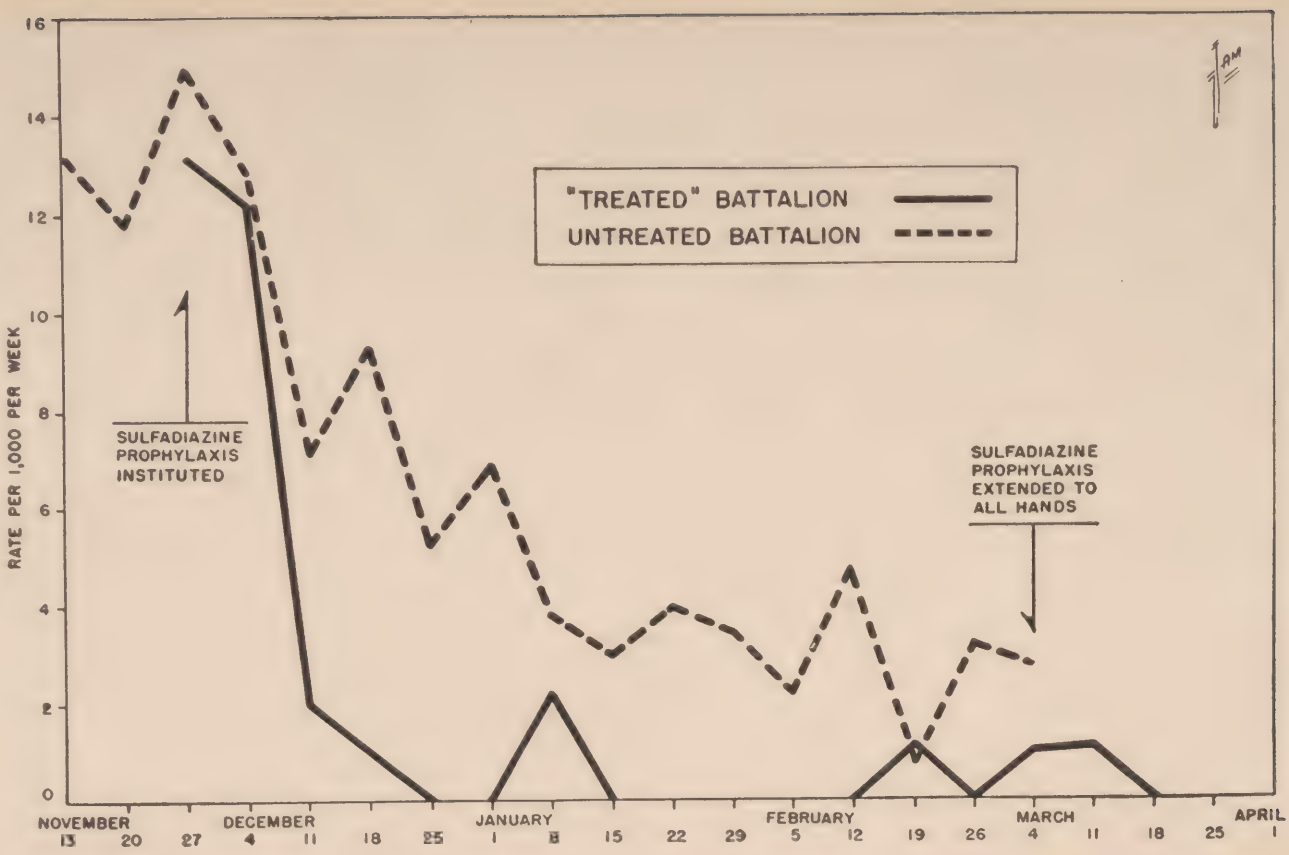
"TREATED" BATTALION
UNTREATED BATTALION
RATE PER 1,000 PER WEEK
SULFADIAZINE PROPHYLAXIS INSTITUTED
SULFADIAZINE PROPHYLAXIS EXTENDED TO ALL HANDS
NOVEMBER
DECEMBER
JANUARY
FEBRUARY
MARCH
APRIL

CHART 33

Infectious Diseases During Winter of 1944 Compared with Winter of 1943

A summary of the data on infectious diseases during January and February of 1943 and 1944 is presented in table 46. This table shows a striking improvement in the health on the station during the period of prophylaxis. The administration of sulfadiazine prophylaxis to half of the personnel lowered the number of susceptibles, and perhaps, this modified the vulnerability of the "herd" to respiratory pathogens.

Relation Between Dosage and Chemotherapeutic Effect

Data on the disease occurring in groups receiving 1 gm. daily, 1 gm. every 2 days, and 0.5 gm. daily are presented in table 47. All three dosage schedules were effective in lowering the incidence of respiratory infections. A daily dose of 1 gm. of sulfadiazine was found necessary to prevent gonorrhea and was most effective in preventing respiratory tract bacterial infections.

Comment

Trainees at this station are more seasoned and of an older age group than those at most Naval training centers. On arrival they are placed in battalions. The housing of these battalions changes throughout their instruction. During a part of their course these men live on a range in the country several miles from the station. Their duties keep them outdoors a large part of the time. Perhaps for these and other reasons these men appear less susceptible to streptococcal infections than men at other Naval training activities situated within a radius of 100 miles.

Although these trainees seem to have some protective mechanism for withstanding Streptococcus hemolyticus, they are, nevertheless, vulnerable to respiratory viruses. This is evidenced by the high rate of influenza in November and December 1943. Sulfadiazine prophylaxis has no apparent effect on virus infections. Sulfadiazine prophylaxis does, however, lower the incidence of respiratory bacterial infections which occur following influenza. This is shown in chart 33.

Conclusions

1. Sulfadiazine prophylaxis prevented bacterial but not virus infections of the respiratory tract. Its effectiveness appeared to depend on the relative prevalence of these two types of infections.

2. Sulfadiazine, 1 gm. daily, prevented between 80 percent and 88 percent of respiratory diseases.

3. Sulfadiazine, 0.5 gm. daily, was somewhat less effective.

4. Sulfadiazine, 1 gm. daily, was 100 percent effective in preventing

meningococcal meningitis and hemolytic streptococcal throat infections at this station.

5. Sulfadiazine, 1 gm. daily, was highly effective in preventing gonorrhea; whereas, 0.5 gm. daily appeared to be of little or no protective value.

6. The mean blood level for the gram daily dose was 2.2 mg. percent and for the daily 0.5 gm. dose was 1.2 mg. percent.

7. Sulfadiazine prophylaxis, irrespective of the schedule of administration, gave rise to mild untoward reactions in 0.3 percent of the cases.

Report 7

Control of Epidemic Upper Respiratory Diseases by Sulfadiazine Prophylaxis

U. S. Naval Air Station Technical Training Center, Memphis, Tenn.

*From Epidemiology Unit 19**

On the first of February 1944 a program of sulfadiazine prophylaxis was instituted at the Memphis Naval Air Technical Training Center at the peak of a streptococcal outbreak. Twenty-four barracks, containing approximately 5,500 students, were selected at random and placed on a regimen of sulfadiazine, 1 gm. daily. Twenty-two barracks, housing about 4,900 students, were chosen to act as an untreated control group. Respiratory infections had been occurring in all these barracks and the severity of streptococcal infections had become disturbing. The morbidity rates for the last week in January (annual admission rates per thousand strength) were: catarrhal fever, 435; tonsillitis and pharyngitis. 341; scarlet fever, 116; rheumatic fever, 4.

Administration

A line officer was assigned to each barracks to supervise the distribution of sulfadiazine tablets. The Epidemiology Unit made spot checks to insure the efficiency of the distribution system. As far as could be determined, each man in the treated group received his drug. Occasionally, it was reported that a man did not swallow his tablets; however, these instances were rare.

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* Participants: Wm. V. Lulow, Lieutenant (MC) USNR; W. W. Kemp, Lieutenant (MC) J. W. Genet, Lieutenant, USNR.

Assistants: E. A. Stone, Pharmacist, USNR: K. M. Hald, PhM1c, USNR; J. H. Dietrick, PhM1c, USNR; C. A. Donohue, PhM2c, USNR; E. M. Douglass. PhM2c, USNR.

Daily records were kept of the number of all ambulatory patients who complained of upper respiratory symptoms. Records of admission were obtained at the sickbay and hospital for all patients with respiratory symptoms, scarlet fever, tonsillitis or pharyngitis, pneumonia, meningitis, and rheumatic fever.

Throat cultures were obtained from every man in the treated group who was admitted to the sickbay or hospital with an upper respiratory tract disease. In addition throat cultures were obtained in 10 percent of the untreated group with similar illnesses. These cultures of hemolytic streptococci were replated on a blood agar slant. Organisms were mailed in pure culture to the Streptococcus Typing Laboratory at the National Naval Medical School and the typing results were returned to this Unit.

Clinical Observations

The results of this streptococcal control program from 1 February to 1 April 1944 are as follows:

Upper Respiratory Tract Infections.—Prior to the institution of the sulfadiazine program, there was a high rate of respiratory infections throughout the entire station. The effect of sulfadiazine prophylaxis on: (a) the incidence of respiratory symptoms as observed at sick call is shown in chart 34; (b) the incidence of admissions to the dispensaries for minor respiratory diseases is shown in chart 35; (c) the incidence of admission to the hospital for severe respiratory diseases is shown in chart 36. These graphs indicate the effectiveness of sulfadiazine prophylaxis in preventing bacterial infections of the respiratory tract.

Scarlet Fever.—Scarlet fever was controlled by sulfadiazine. Within the first week there was a sharp drop in the incidence of scarlatina in the group receiving prophylaxis. Only 3 cases occurred in March in the treated group; whereas 23 cases appeared among the controlled personnel. Morbidity rates are shown in chart 37. From our experience during the first 9 weeks of the study, it appeared that fairly conclusive evidence was obtained as to the effectiveness of sulfadiazine prophylaxis in the prevention of scarlet fever.

Tonsillitis, Pharyngitis, and Catarrhal Fever.—The striking difference in the incidence of these diseases observed between the treated and untreated groups is shown in charts 38 and 39. Sulfadiazine reduced the incidence of these illnesses beginning with the first week of the prophylaxis program.

Meningitis.—Meningitis was completely controlled. During the 2 months of this study, seven cases of meningitis occurred among untreated personnel; none appeared among the treated group.

Rheumatic Fever.—Chart 40 shows the incidence of rheumatic fever during February and March. The program of sulfadiazine prophylaxis

CHART 34

All Upper Respiratory Diseases
Sulfadiazine Prophylaxis-NATTC-Memphis, Tenn.
DAILY SICK-CALL REPORT
(Cases per Thousand per Week)
Solid Line - Treated (1 gram sulfadiazine daily)
Broken Line - Untreated

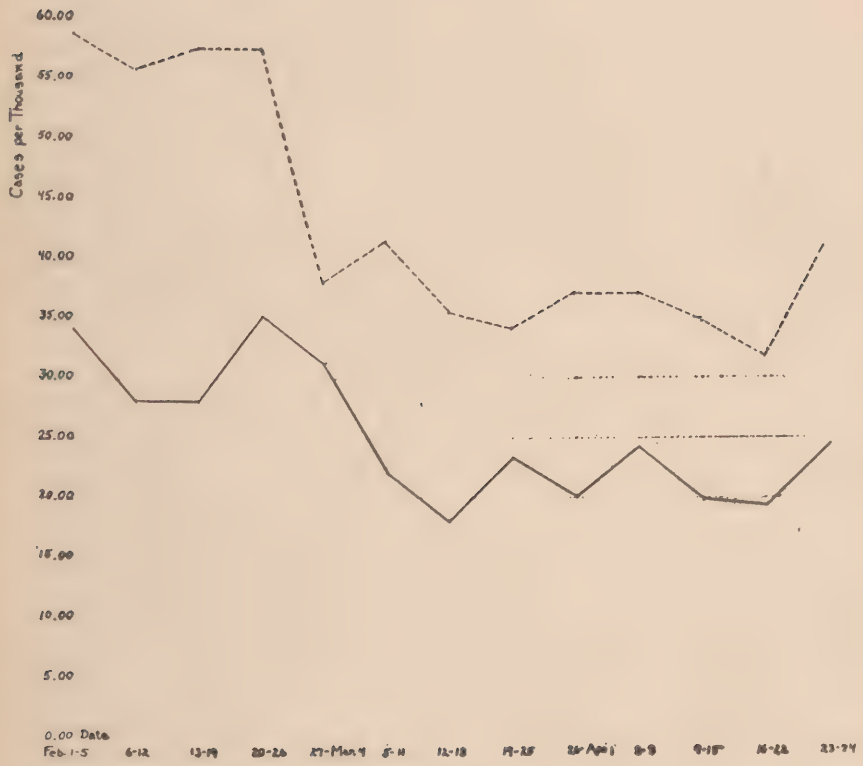

CHART 35

Sulfadiazine Prophylaxis-NATTC-Memphis, Tenn-1944
-ADMISSIONS to DISPENSARY-
(Rate per Thousand per Week)
Solid Line - Treated with one gram of sulfadiazine daily - Feb 1, 1944 through April 30, 1944
Broken Line - Untreated-from Nov 22, 1943 through Apr 30, 1944

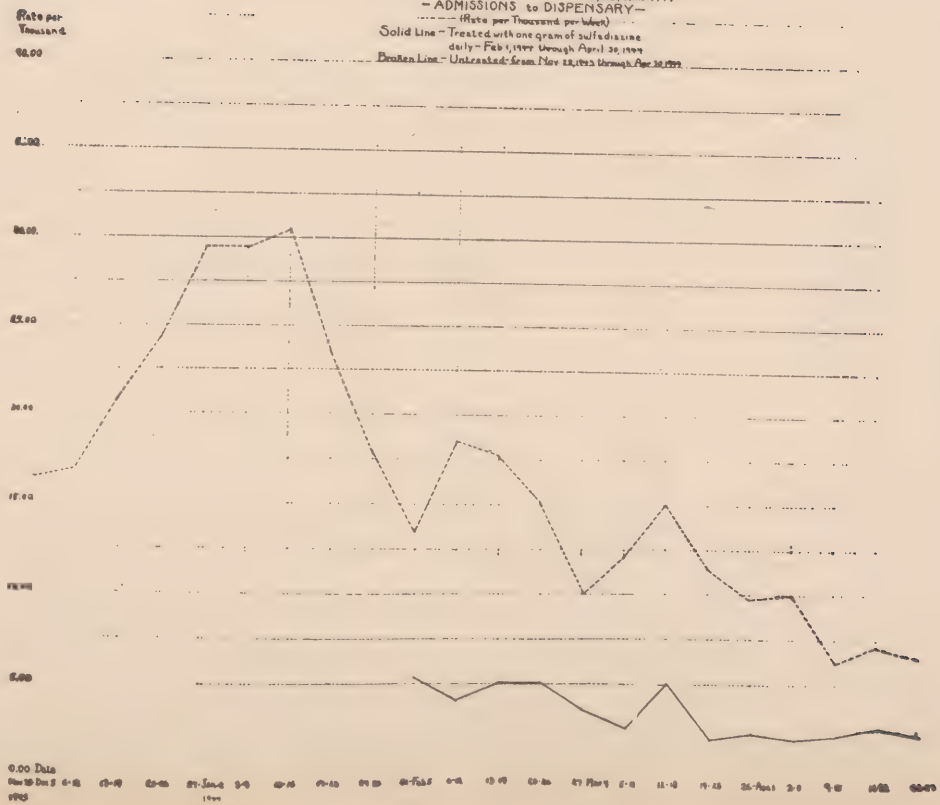

CHART 36

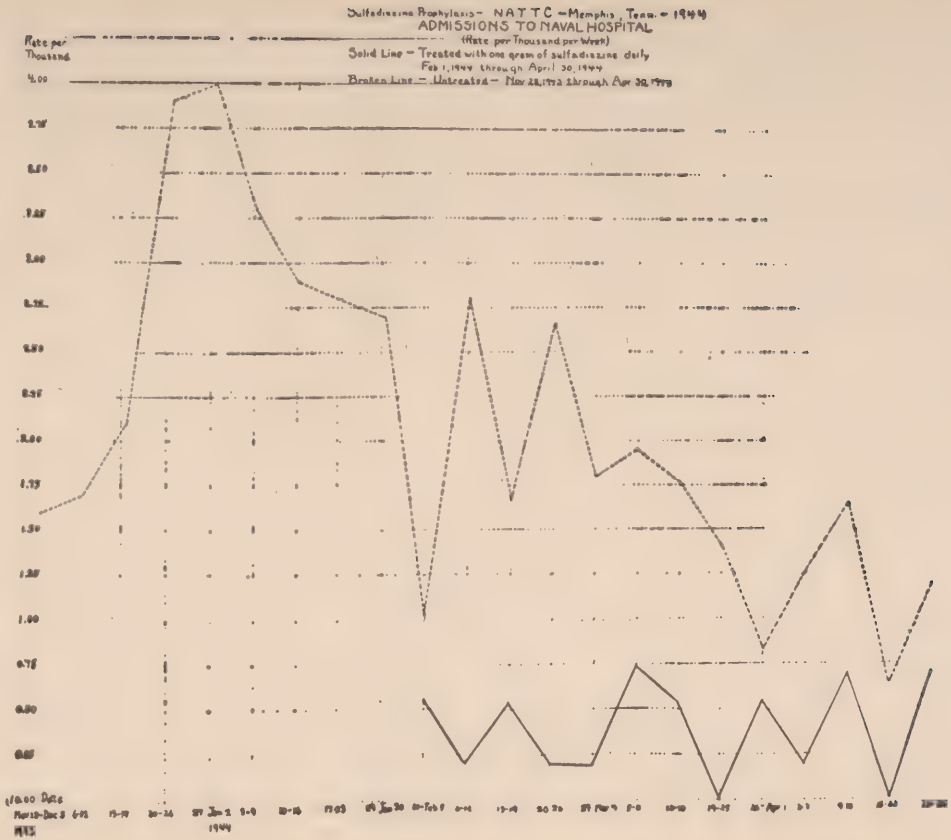
Sulfadiazine Prophylaxis – NATTC – Memphis, Tenn. – 1944
ADMISSIONS TO NAVAL HOSPITAL
(Rate per Thousand per Week)
Solid Line – Treated with one gram of sulfadiazine daily
Feb 1, 1944 through April 30, 1944
Broken Line – Untreated – Nov 28, 1943 through Apr 30, 1944
Rate per Thousand
4.00
2.50
2.00
1.50
1.00
0.50
1944

CHART 37

Sulfadiazine Prophylaxis – NATTC – Memphis Tenn. – 1944
– Scarlet Fever –
(Rate per Thousand per Week)
Solid Line – Treated with 1 gram of sulfadiazine daily – Feb 1, 1944 through Apr 30, 1944
Broken Line – Untreated Nov 28, 1943 – through Apr 30, 1944

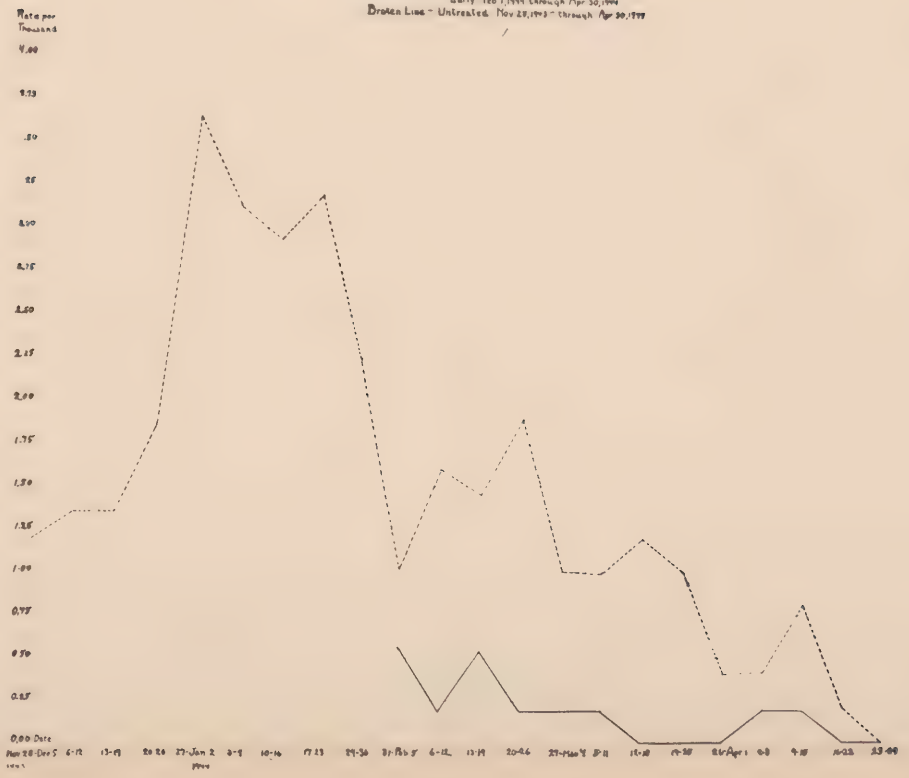

CHART 38

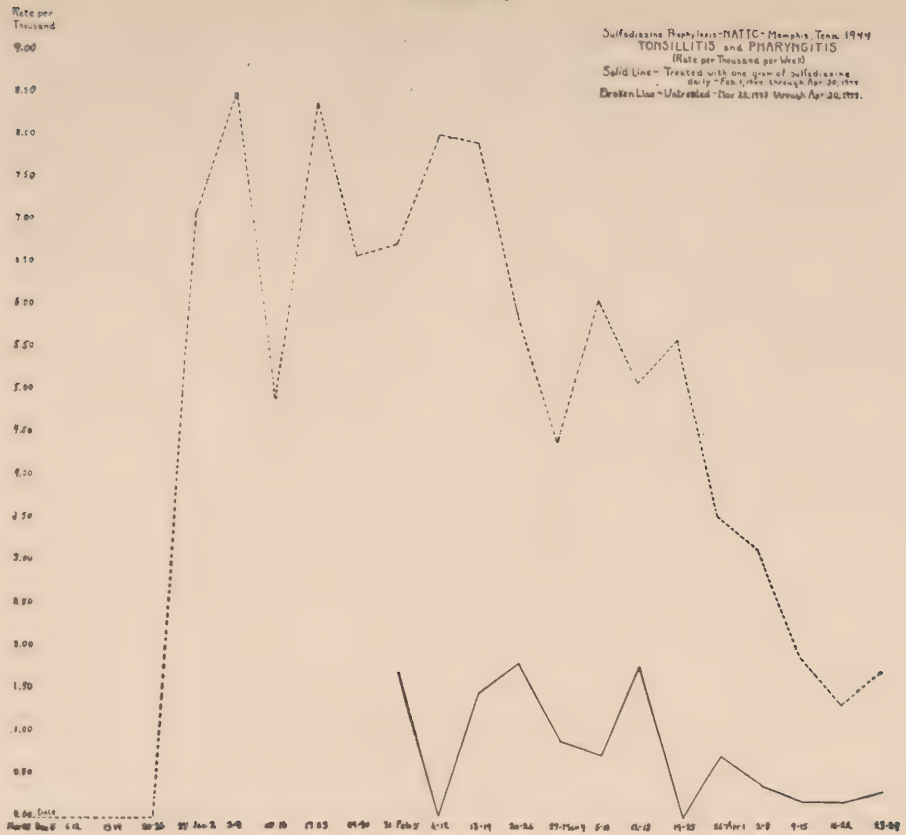
Rate per Thousand
Sulfadiazine Prophylaxis-NATTC-Memphis, Tenn. 1944
TONSILLITIS and PHARYNGITIS
(Rate per Thousand per Week)
Solid Line - Treated with one gram of sulfadiazine daily - Feb. 1944 through Apr. 30, 1944
Broken Line - Untreated - Nov. 22, 1943 through Apr. 30, 1944.

CHART 39

Sulfadiazine Prophylaxis - NATTC - Memphis - Texas - 1959

- CATARRHAL FEVER -

(Rate per Thousand per Week)

Solid Line - Treated with 1 gram of sulfadiazine daily - Feb. 1, 1959 through Apr. 30, 1959

Broken Line - Untreated - Nov. 23, 1958 through Apr. 30, 1959

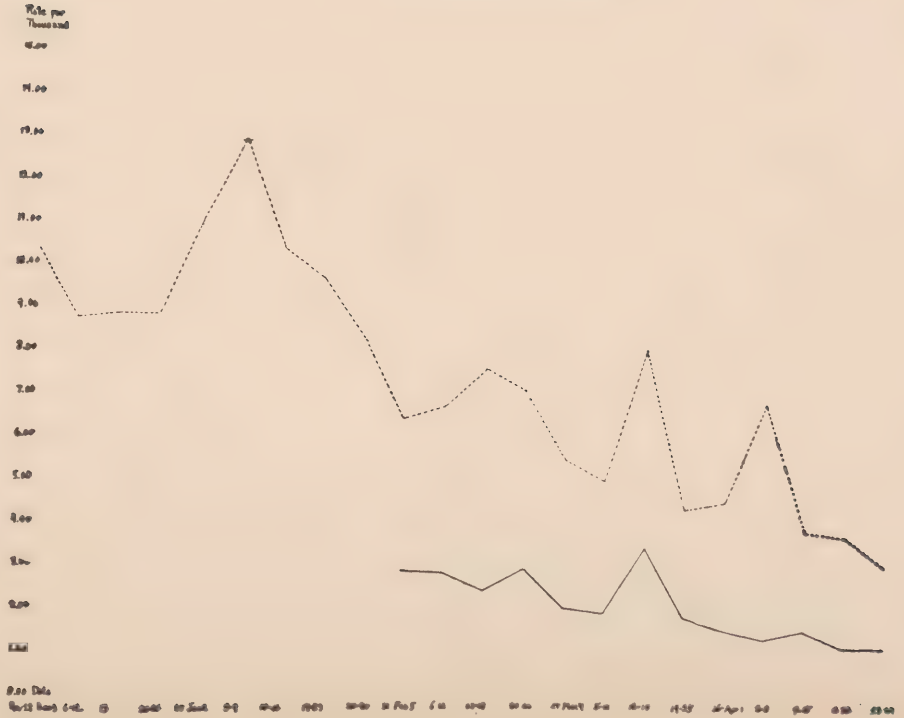

CHART 40

Sulfadiazine Prophylaxis – NATTC – Memphis, Tenn 1944
– RHEUMATIC FEVER –
(Rate per Thousand per Week)
Solid Line – Treated with one gram of sulfadiazine daily – Feb 1, 1944 through Apr 30, 1944
Broken Line – Untreated – Nov 28 through Apr 30

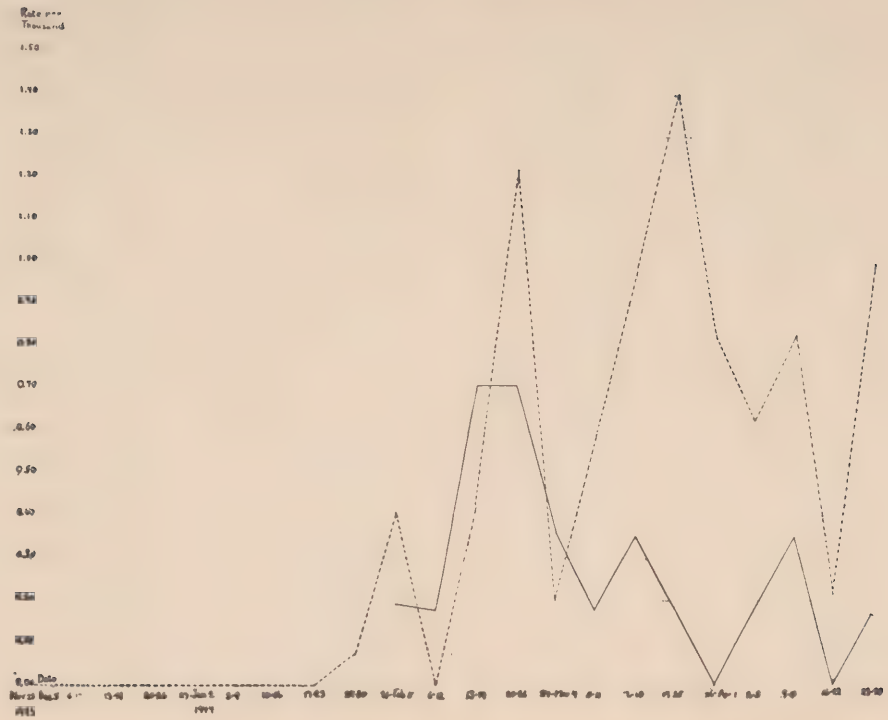

TABLE 48.—*Rheumatic fever with rates per thousand per week: treated and untreated groups*

Date	Treated		Untreated	
	No. cases	Rate per 1,000	No. cases	Rate per 1,000
Feb. 1–6	1	.19	2	.41
6–12	1	.18	0	.00
13–19	4	.71	2	.42
20–26	4	.71	6	1.22
Feb. 27–Mar. 4	2	.36	1	.20
Mar. 5–11	1	.18	3	.59
12–18	2	.35	5	.98
19–25	1	.18	7	1 .4
26–April 1	0	.00	4	.83
Total	16		30	

TABLE 49.—*Drug reactions classified as to type*

Description	Number of cases	Average amount of drug ingested (grams)
Generalized morbilliform of punctate rash	41	26
Urticaria	* 12	19
Edema	* 3	23
Headache, nausea and vomiting	4	43
Agranulocytosis	1	58
Stomatitis	1	6

* 1 case exhibited both edema and urticaria.

had been designed to reduce the incidence of bacterial respiratory infections, particularly those caused by hemolytic streptococci. The institution of the program was accompanied by a significant drop in the number of respiratory infections. This was followed by a progressive disappearance of rheumatic fever in the treated group. Table 48 gives the number of cases and the rates in the treated and untreated groups, by weeks, since the program of sulfadiazine prophylaxis was begun.

The first month of sulfadiazine prophylaxis could not have been expected to reduce the number of cases of rheumatic fever because the hemolytic streptococcal infections which precipitated the February cases of rheumatic fever had already occurred. In the first 4 weeks of prophylaxis, each group had 10 cases; whereas during the last 5 weeks, only 6 cases appeared in the treated group and 20 cases appeared in the untreated group.

Pneumonia.—Sulfadiazine prophylaxis had little if any effect on the rate of pneumonia. Cases of pneumonia at this station during February and March were diagnosed as primary atypical pneumonia with few exceptions.

Gonorrhea.—Following the institution of sulfadiazine prophylaxis, it was noted that the incidence of gonorrhea was greatly reduced. The rates of infections among all Negro personnel receiving prophylaxis were at the lowest point ever seen on this station.

Drug Reactions

Drug reactions during the 2 months of this study totaled 61. Of these, 1 case appeared to be granulocytopenia. The patient is still under study and is making an uneventful recovery. The data on sulfadiazine reactions are tabulated in table 49.

Results of Typing

Forty-eight strains of hemolytic streptococci were sent to the Laboratory at the National Naval Medical School. The most prevalent serologic types were 19 and 17. Types 3, 1 and 36 were recovered from several throats. Other types present were 2, 5, 6, 14, 24, and 41.

Conclusions

The following conclusions are drawn from the observations made during the administration of 1 gm. of sulfadiazine daily to half of the enlisted personnel at Memphis Naval Air Technical Training Center in February and March, 1944.

1. Mild bacterial respiratory tract infections, not requiring hospitalization, were reduced in incidence.
2. Tonsillitis and pharyngitis were markedly reduced in incidence.
3. Scarlet fever was almost entirely prevented.
4. Rheumatic fever persisted during the first 4 weeks of prophylaxis, then declined progressively and was not observed during the last week of this study.
5. Meningitis (meningococcal and streptococcal) was entirely prevented.
6. Gonorrhea was greatly reduced in incidence.
7. Pneumonia (atypical) was not prevented.
8. Drug reactions occurred in 0.6 percent of men treated over a period of 9 weeks. All reactions but one were mild.

Report 8

Mass Prophylaxis of Respiratory Disease
U. S. Naval Air Technical Training Center, Norman, Okla.

*From Epidemiology Unit 43**

The Streptococcal Control Program instituted at the Norman base was an attempt to explore the efficacy of sulfadiazine in mass prophylaxis during a severe outbreak of streptococcal diseases. It was hoped that some rational evaluation of the drug in this role might be made on the basis of clinical and epidemiologic data without recourse to elaborate laboratory facilities. The data reported herein consequently represent the observations of a group of clinical workers.

Methods

Four groups, designated hereafter as groups A, B, D, and E, were selected for observation in this program. Each group comprised from 2,000 to 3,000 men, enlisted personnel. Inasmuch as no attempt was made at selection within groups, it may be presumed that there was no significant difference in age, geographic origin, or racial stock. Each group consisted primarily of trainees in aviation ordnance, metalsmith work and mechanics, and was subjected to the same or similar hazards of weather and occupation. Although each group was quartered in its own regimental area, these regimental areas were separated only by a dividing street. Although the areas were adjacent, there was little opportunity for mingling of trainees from different groups or areas; the staggering of classes, duty, and liberty undoubtedly reduced to an insignificant factor the mingling of men from different areas. In only one respect did the groups represent a specific difference: Group D was com-

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posed exclusively of Marines; whereas members of the other groups belonged to the Navy personnel.

Observations concerning the respiratory health of these trainees were made at the dispensaries of the station. Sick Call for respiratory disorders was held at only two of the dispensaries; a daily census of these calls was recorded by analyzing the diagnosis from the sick-call chits of new patients. The majority of the moderately ill patients were admitted to the sickbay of Dispensary 34 which was staffed by members of the Epidemiology Unit. The acutely ill patients were admitted to the U. S. Naval Hospital. These patients were visited daily by some member of the Unit to confirm diagnoses and take cultures. In this manner, a reasonably accurate morphologic diagnosis and record of disease of the respiratory tract could be made. These diagnoses included coryza, rhinitis, pharyngitis, tonsillitis, streptococcus infection of the throat, cerebrospinal fever, catarrhal fever, rheumatic fever, and the various kinds of pneumonia. The four groups were observed for 3 weeks to ascertain a baseline of health or morbidity for trainees. As a control, group A was selected not to receive the drug.

Each of the personnel of the three remaining groups B, D, and E received 1 gm. of sulfadiazine daily after 17 February 1944. Many administrative details, some of which were not anticipated, presented themselves and the most vigilant supervision was indicated. Close cooperation with the regimental commanders was essential to reduce the errors to a minimum. Some of these are enumerated and described in order to disclose the pitfalls in the proper evaluation of this type of clinical research.

The untreated group A was neither informed of its control role nor were blank pills issued to them. The ready accessibility of the sulfonamides makes self-medication of minor respiratory disease not exceptional; several such instances were disclosed and it is impossible to evaluate that factor in the morbidity rate of the control group. Among the groups receiving the drug as a prophylactic, all sorts of subterfuge were uncovered by tactful investigation. Examination of the oral cavity following ingestion of the tablets was employed at some of the musters but such a procedure becomes impracticable as a daily procedure among 6,000 or more men. Similarly, week-end liberty inevitably increased the number of instances of noncooperation. The latter difficulty was partly obviated by the administration of 2 gm. of the drug each Saturday to all men having week-end liberty. Blood chemical determinations were not made to ascertain the presence of a residual effective level before the next regular dose was administered. Fear of untoward reactions was not a significant motive among those failing to cooperate. On the other hand, the project did not have the influence of fear of an epidemic in securing cooperation.

Laboratory studies consisted of taking throat cultures and, in a few instances, the culture of otic and pulmonary exudate. Except in cases of typical pneumonia, principal interest in these cultures was in the identification and typing of hemolytic streptococci. Throat cultures were taken from all patients admitted to the sickbay or hospital from groups B, D, and E. Sampling of group A was accomplished by taking cultures from approximately 10 percent of the patients in this group.

TABLE 50.—*Consolidated rates for respiratory infections before and during prophylaxis*

	Three control weeks		Twelve prophylaxis weeks	
	A	B-D-E	A*	B-D-E**
Respiratory complaints	241.0	233.2	452.00	227.4
Respiratory illnesses admitted to dispensaries	53.2	42.4	63.60	29.4
Respiratory illnesses admitted to hospital	12.1	8.24	11.64	7.09
Scarlet fever	6.05	3.12	5.22	2.53
Tonsillitis or pharyngitis or both	24.2	24.6	28.60	7.97
Pneumonia	0.81	1.43	7.23	7.20

* A was control group. ** B-D-E received chemoprophylaxis.

Results

The accumulated data are shown in table 50. A more striking analysis may possibly be made by referring to the weekly morbidity rates as judged by the number of patients visiting the dispensaries with symptoms of respiratory disease. These rates are shown in table 51; the rates for the corresponding periods in 1943 are shown in the same table for comparison. The weekly rates for 1944 are shown in chart 41. Although there occurred a general reduction in the morbidity rates about the time the prophylaxis was instituted, a sharp reduction in the rates of groups B, D, and E was observed within 1 week of the institution of this program. This reduction was maintained throughout the period of prophylaxis. Subjecting these figures to significance tests, it is shown unequivocally that some factor other than chance is responsible for the disparity in attack rates between the two groups after 17 February.

A similar difference is shown in the attack rates for scarlet fever and acute pharyngitis (including tonsillitis). These diseases are due almost exclusively to organisms which are usually sensitive to the inhibiting influence of the sulfonamides; therefore, this comparison represents a more decisive trial of the drug than the inclusion of all respiratory disease. The attack rate of these diseases was more than 3 times as great among the trainees in group A as among those receiving the prophylactic drug; in this instance also such a difference in attack rates is not accidental.

TABLE 51.—*Respiratory infections: attack rate per thousand*

	26 Jan.–1 Feb.		2 Feb.–8 Feb.		9 Feb.–15 Feb.		16 Feb.–22 Feb.		23 Feb.–29 Feb.		1 Mar.–7 Mar.	
1943	96.0		78.3		75.8		82.3		67.2		75.4	
Area	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A
1944	106.00	87.20	64.20	76.70	64.00	76.10	33.80	50.30	22.60	48.30	17.50	30.50
	8 Mar.–14 Mar.		15 Mar.–21 Mar.		22 Mar.–28 Mar.		29 Mar.–4 Apr.		5 Apr.–11 Apr.		12 Apr.–18 Apr.	
1943	69.8		69.2		44.6		54.2		39.3		27.1	
Area	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A
1944	17.20	37.84	20.10	32.90	20.62	48.20	17.40	40.25	17.10	42.00	15.75	32.60
	19 Apr.–25 Apr.		26 Apr.–2 May		3 May–9 May		10 May–16 May		17 May–23 May		24 May–30 May	
1943												
Area	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A	B-D-E	A
1944	13.4	27.4	15.39	26.65	16.2	25.77	16.7	33.3	19.6	22.0	19.7	26.4

Areas B-D-E received chemoprophylaxis from February 17 to May 30.
Area A served as a control group.

The number of infections due to the Neisseriae was too small to warrant comparison. Five cases of meningococcal meningitis were observed among the 10,000 odd trainees during the 3 weeks' control period before the drug was administered prophylactically. In the succeeding 10 weeks, a single case was observed, and the patient was admitted to the dispensary a few hours after the first distribution of sulfadiazine.

It will be observed from table 50 that the number of cases of pneumonia increased during the period of sulfadiazine administration; moreover, the pneumonia morbidity rate increased in each group without any apparent pattern of increase. Further inspection of this group of cases discloses an explanation for this apparent paradox. Of the entire series of pneumonia cases, only five were shown to be of bacterial origin; pneumococci of Type I were found in 2 instances; Type II in 2 instances, and Type V in a single case. Most of the remaining cases of pneumonia conformed to the clinical and roentgenologic description of primary atypical pneumonia, cause unknown, and none of these showed a satisfactory clinical response to the sulfonamides. If the causative agent of this group is a virus, as many investigators believe, there is little reason to expect an inhibiting effect from the sulfonamides.

Bacteriology

The results of the bacteriologic studies, as they pertain to the streptococcus, are shown in table 52. There are insufficient typings to warrant positive generalizations. It appears that during this period Type 17 was the most prevalent. No single type is found regularly as the causative agent in any given clinical entity. It might be significant that in only 7 instances were hemolytic streptococci isolated from pneumonia patients and in 2 of these instances the patients undoubtedly had typical pneumococcal pneumonia.

TABLE 52.—*Serologic types of group A hemolytic streptococcus recovered from respiratory infections*

Disease	Types												Not group A
	1	3	6	12	14	17	18	19	24	36	46	A–?	
Bronchitis pneumonitis	1				1		1						4
Cat. fever			1					1		2	1	1	3
Scarlet fever		1		1		3				1		1	2
Mastoiditis otitis media			1			3							
Pharyngitis	1		2		1	2			1			1	2
Tonsillitis, acute	1		2			2		1				1	
Rheumatic fever								1					
Total	3	1	6	1	2	10	1	3	1	3	1	4	11

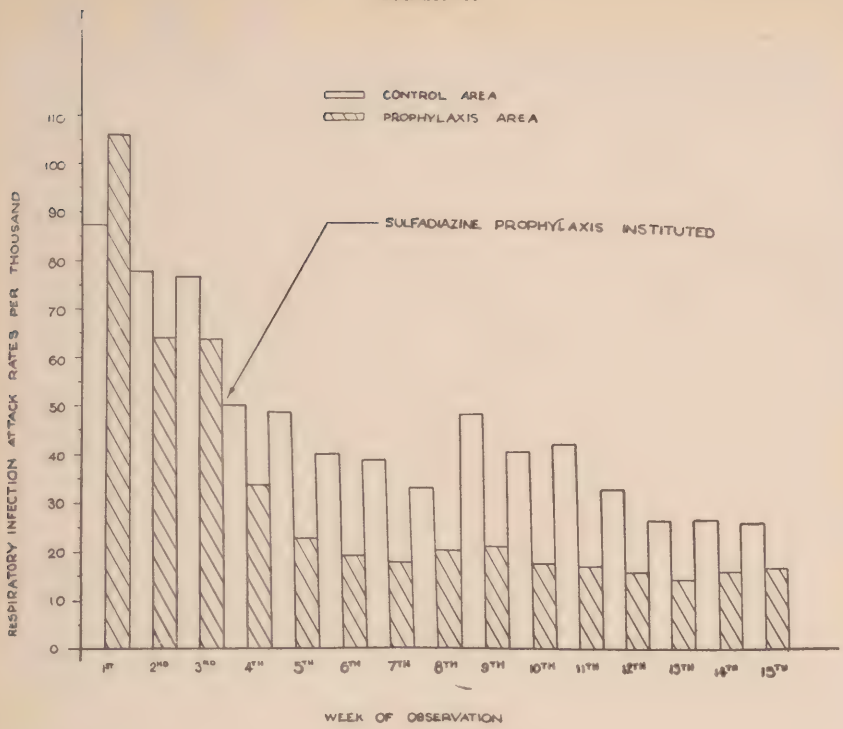
Untoward reactions were infrequent following the daily ingestion of the drug. No deaths occurred among the trainees during the period of observation. All patients who presented symptoms suggesting an intolerance of the drug were seen by a member of the Epidemiology Unit. In several cases patients were interviewed and examined who complained of gastro-intestinal disturbances. In each case, some other factor was disclosed and the drug was not discontinued in a single instance because of real or fancied gastro-intestinal symptoms. Cases of toxicity involving the hematopoietic system were not observed.

As might be expected, the only significant untoward reactions seen were those manifested by a skin eruption. Fifty-one trainees were examined who presented local or generalized dermatitis. For the greater part, these rashes were morbilliform, and in a few instances, it was almost impossible to differentiate the eruption from German measles. Likewise in an occasional case, the differential diagnosis from scarlet fever was perplexing on an exclusively morphologic basis. Two cases resembled the erythema nodosum rash characteristic of sulfathiazole dermatitis; in neither case did the skin present a subcutaneous nodule on palpation. Conjunctival injection was seen in several instances accompanying a generalized eruption.

Because of the pleomorphism of sulfonamide skin reactions, an attempt was made to confirm the original impression by reproducing the lesion after an interval of from 7 to 14 days. Of these 51 cases, the dermatitis was reproduced later in 17 instances by the administration of small daily amounts of the drug. In most cases, the eruption reappeared after 1 or 2 gm. given in daily doses of 0.5 gm.-1 gm. It may be speculated that the remaining patients had been desensitized by the further or continued ingestion of the drug. Until some reliable immuno-chemical tests are available, the question of sensitivity to the sulfonamides will probably remain controversial.

Further observations were made concerning sulfonamide sensitivity in those patients who had reproducible skin lesions. After an interval of from 1 to 4 weeks, fifteen of these patients were administered the monomethyl derivative (sulfamerazine) of sulfadiazine in daily doses of 1 gm. At the time of the completion of this program, only three had shown a reaction to this derivative. This observation is in agreement with the observations of others that these so-called sensitivities to the sulfonamides are specific and show little cross-reaction, even to isomeric forms. Such observations emphasize not only the urgency but also the value of informing the patients of their reactions. It seems equally important to record these observations in the individual health record, so that needless and possibly serious reactions might be prevented at a later occasion.

CHART 41



Conclusions

1. The administration of 1 gm. of sulfadiazine daily for 12 weeks to approximately 8,000 Naval trainees effected a significant reduction in the incidence of respiratory disease.

2. This effect was not noted for virus diseases or those suggesting virus origin.

3. The daily administration of 1 gm. of the drug caused skin rashes in not more than 51 trainees, an incidence of considerably less than 1 percent.

4. No severe untoward effects were seen following the daily administration of 1 gm. of sulfadiazine and only 17 trainees were excused from the program because of dermal reactions.

Report 9

The Streptococcal Control Program Navy Pier, Chicago

*From Epidemiology Unit 89**

A program for the prevention of respiratory diseases, especially those caused by Streptococcus hemolyticus, was initiated 8 February 1944. On this date the indications for a Streptococcal Control Program at this Naval activity was striking. During December 1943 more than 25 percent of the station's complement had been admitted to the sick list with respiratory infections; a total of 27,966 man-days, 10 percent of the available manpower, was lost. The incidence of these infections continued to be high in January, and a large number of men developed rheumatic fever. By 1 February 1944 the annual admission rate had reached extraordinary heights: for rheumatic fever, 70; for scarlet fever, 171; for tonsillitis, 426; and for catarrhal fever, 988. The urgency of the situation and the expectancy of an increase in the prevalence of streptococcal infections during February and March were strong indications for placing all enlisted personnel on a program of sulfadiazine prophylaxis.

It was believed that a controlled study would be unwise and that streptococcal rates at other Naval activities in the Chicago area would serve as an indicator of the prevalence of these infections. The present report deals with the effect of sulfadiazine prophylaxis on respiratory infection rates during February and March, 1944 at Navy Pier, Chicago.

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* Participants: Douglas S. Damrosch, Lieutenant (MC) USNR; Byron D. Casteel, Lieutenant (MC) USNR; R. G. Lapenta, Lieutenant (MC) USNR (Epidemiology Unit 13); George C. Morris, Lieutenant (jg), H-V(S) USNR.

Assistants: P. R. Carter, PhM1c; USNR; W. F. Alston, PhM2c, USNR; C. C. Ball, PhM2c, USNR.

Acknowledgements: To Captain T. H. Taber, (MC) USN; Captain H. A. Noreen, (MC) USN; and the Medical Officers at the Navy Pier for their cooperation in the administration of the program.

Administration

First, all the details for administering sulfadiazine prophylaxis were explained to the line officers in charge of the several companies into which the station personnel is divided. A supply of sulfadiazine was delivered to the regimental office weekly and thence to the various company commanders. Each man on the station was then ordered to take 1 gm. of sulfadiazine in a single daily dose. This was issued by company officers or responsible petty officers at an hour when the company could be mustered conveniently; most companies elected early morning, just prior to the beginning of classes. Two grams of sulfadiazine were administered each Saturday and none was given on Sunday. Incoming draftees were automatically started on the drug regimen on arrival. Through their officers, all men were instructed to report immediately to the sickbay on the appearance of a rash or when noticing any change in their general health. In the sickbay, the medical officers of the station referred all patients with probable drug reactions to a medical officer of the Unit who attended daily sick call.

Examinations of Throat Flora

Throat cultures were studied of 40 men who contracted respiratory infections during this 2-month period; in 31 of these there were no hemolytic streptococci in the throat flora; in 9 this organism was found in cultures of the nasopharynx; 5 of these were diagnosed as catarrhal fever; 3 tonsillitis, acute, and 1 scarlet fever. The strains of hemolytic streptococci isolated from these men were shipped to the National Naval Medical Center where the serologic types were identified as 17, 3, 30, 1, 5, and 36.

Study of Untoward Reactions to Sulfadiazine

Each patient with symptoms attributable to sulfonamide was examined and then given a card excusing him from the prophylactic program. In from 10 days to 2 weeks he was called back for retesting. This was done by having him report on 4 consecutive days. On the first day the patient was given sulfadiazine, 0.5 gm., and on the following day, 1 gm. If any toxic manifestation appeared within this period, the patient was removed from the program and an entry was made in his health record indicating that he was sensitive to sulfadiazine. If no untoward reaction occurred, his card was taken and he was again placed on the sulfadiazine program.

Altogether 131 men reported to sickbay where they were studied for possible drug reactions. Histories were taken to determine their previous experience with sulfonamides, the length of time on the Streptococcal Control Program, and previous manifestations of idiosyncrasy. Urine examinations and complete blood counts were made; all proved to be normal.

Eight of this group had skin diseases not associated with sulfonamides (psoriasis, pityriasis, scabies, eczema, acne vulgaris, and fungus infections). Sixty-three who were apparently drug-sensitive were retested with sulfadiazine. Twenty-eight were found to be sensitive to the drug. Thirty-five remained symptom-free and were returned to the program. None of these has reported back with drug reactions. On the basis of those retested, it is probable that approximately one-half of those originally seen were actually sensitive, a rate of 0.3 percent.

The toxic manifestations to sulfadiazine varied considerably. The most common one seen was a maculopapular erythematous rash (accompanied by pruritus in half the cases), particularly prominent on the flexor surfaces of the extremities, medial aspect of the thighs, and on the lateral aspect of the thorax. The next most common manifestation was a finely granular scarlatiniform rash with similar distribution. In four cases this type of rash was accompanied by chilly sensations, nausea, and fever ranging from 102° F. to 104° F. In all cases fever and symptoms subsided within 24 hours after sulfadiazine administration was discontinued. A number of cases of urticarial reactions were also seen. In two cases there was a rash limited to the legs and characterized by numerous small, discrete purpuric spots.

There was no correlation between the severity or type of reaction and the number of days on the drug program. About 50 percent of the sensitive patients had received therapeutic doses of sulfonamides in the past and 73 percent of these had experienced toxic manifestations during therapy. Three had multiple idiosyncrasies.

Results

The institution of sulfadiazine prophylaxis at the Navy Pier was followed by a rapid fall in the incidence of disease. The scarlet fever rate, for example, fell weekly to 70, 45, and during the third week to zero. The rheumatic fever rate rose during the first week to 87 and then fell progressively to 45, 45, 19, and 6. This improvement was not to be expected during February and March, and the weekly rates for scarlatina and rheumatic fever at other Naval activities in Chicago rose during this period.

Four charts will serve to illustrate the effectiveness of sulfadiazine at the Navy Pier: Chart 42 on the daily admissions to the sick list; chart 43 on morbidity from respiratory infections, chart 44 on the incidence of scarlet fever and rheumatic fever; and chart 45 on the morbidity from respiratory infections in comparison with five other activities in the Chicago area.

Chart 42 shows a day-to-day record of admissions to the sick list at the Navy Pier for the following diseases: Tonsillitis, pharyngitis, catarrhal fever, scarlet fever, rheumatic fever, pneumonia (all forms), acute

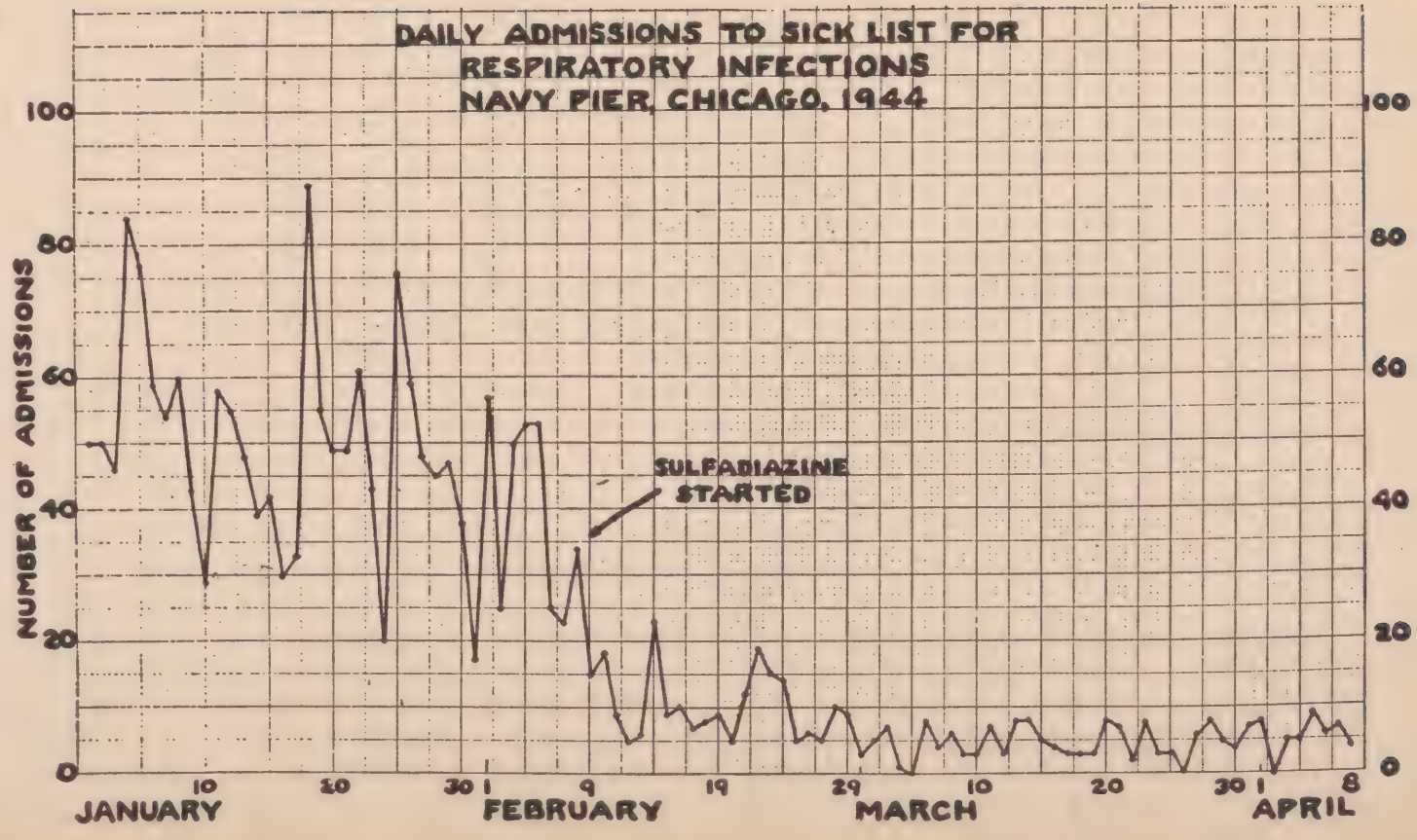

DAILY ADMISSIONS TO SICK LIST FOR
RESPIRATORY INFECTIONS
NAVY PIER, CHICAGO, 1944
NUMBER OF ADMISSIONS
0
20
40
60
80
100
SULFADIAZINE
STARTED
10
20
30
1
9
19
29
10
20
30
1
8
JANUARY
FEBRUARY
MARCH
APRIL

CHART 42

CHART 43

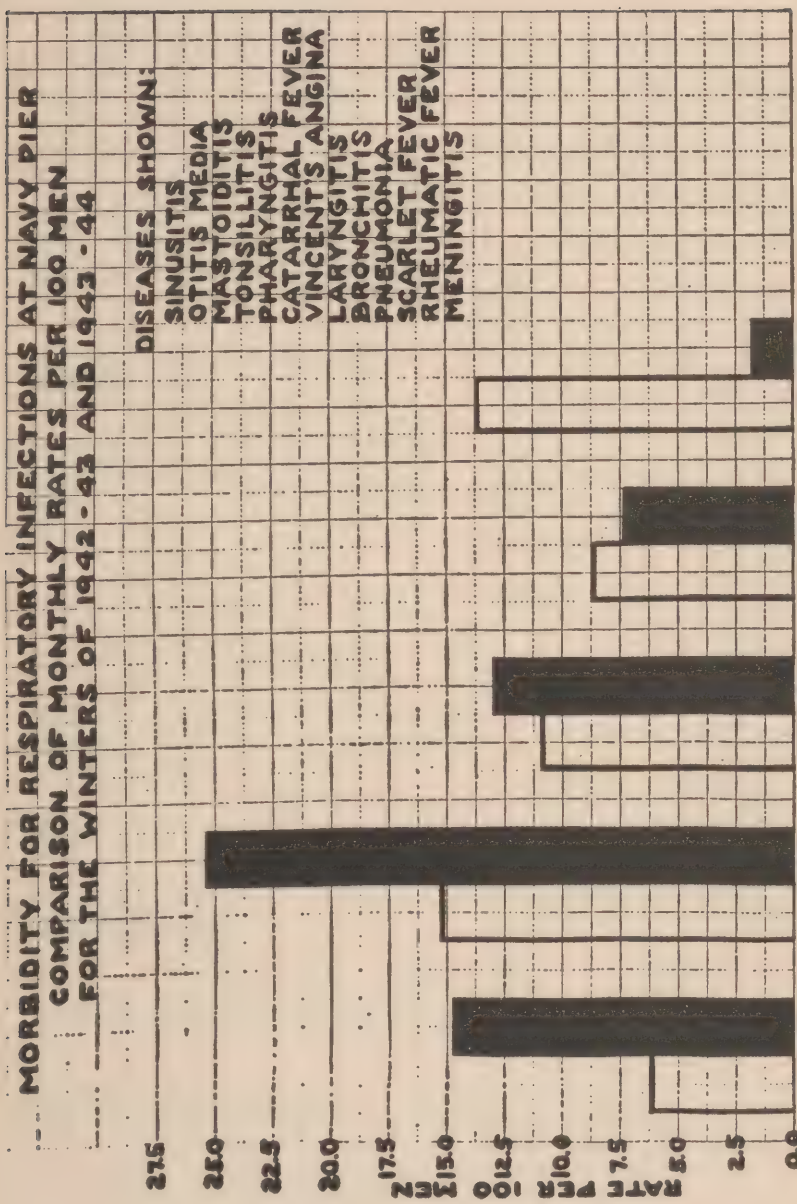

MORBIDITY FOR RESPIRATORY INFECTIONS AT NAVY PIER
COMPARISON OF MONTHLY RATES PER 100 MEN
FOR THE WINTERS OF 1942-43 AND 1943-44
DISEASES SHOWN:
SINUSITIS
OTITIS MEDIA
MASTOIDITIS
TONSILLITIS
PHARYNGITIS
CATARRHAL FEVER
VINCENT'S ANGINA
LARYNGITIS
BRONCHITIS
PNEUMONIA
SCARLET FEVER
RHEUMATIC FEVER
MENINGITIS
RATE PER 100
27.5
25.0
22.5
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
42 43 NOV.
42 43 DEC.
43 44 JAN.
43 44 FEB.
43 44 MAR.

CHART 44

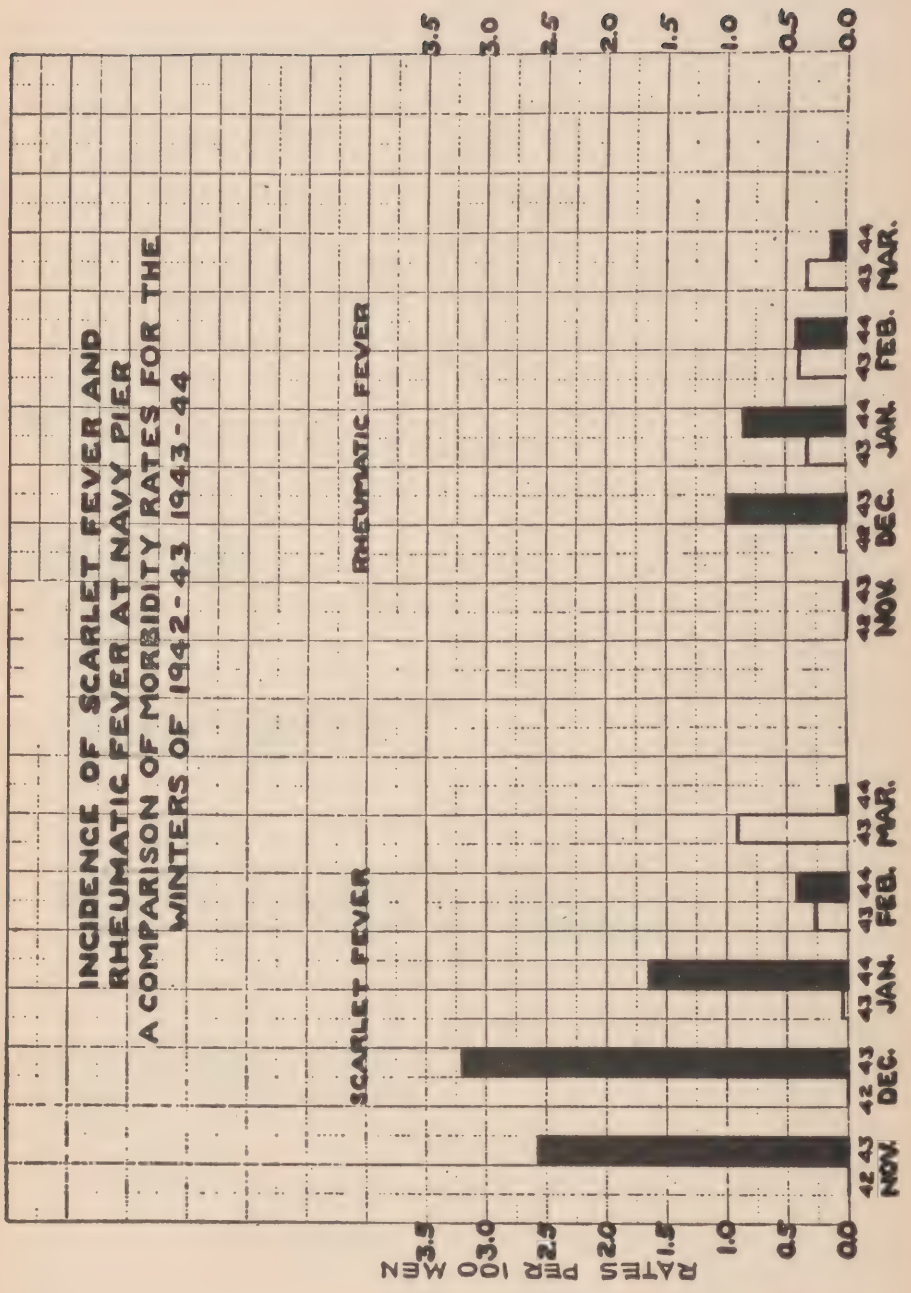

INCIDENCE OF SCARLET FEVER AND
RHEUMATIC FEVER AT NAVY PIER
A COMPARISON OF MORBIDITY RATES FOR THE
WINTERS OF 1942-43 1943-44
SCARLET FEVER
RHEUMATIC FEVER
RATES PER 100 MEN
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
42 43 NOV.
42 43 DEC.
43 44 JAN.
43 44 FEB.
43 44 MAR.

CHART 45

MORBIDITY RATES FOR RESPIRATORY INFECTIONS AT NAVY PIER AND OTHER NAVAL ACTIVITIES IN CHICAGO DURING THE WINTER OF 1943-44
NAVY PIER
OTHER ACTIVITIES
WRIGHT JUNIOR COLLEGE PRE-RADIO
UNIV. OF CHICAGO SIGNAL & RADIO
NORTHWESTERN UNIV. SIGNAL & RADIO
NAVAL ARMORY
MIDSHIPMEN'S SCHOOL
RATES PER 100 MEN
0
2
4
6
8
10
12
14
16
18
20
22
24
26
NOVEMBER
DECEMBER
JANUARY
FEBRUARY
MARCH
WRIGHT J.C.
U. of CHICAGO
N.W.U.
ARMORY
MDN.

sinusitis, laryngitis, acute otitis media, Vincent's infection, acute bronchitis, acute pyogenic meningitis, and acute mastoiditis. The points of this chart represent absolute numbers and not rates. There was a rise in the average strength of the station in February over January, and a small decrease in strength in March.

Chart 43 shows the monthly morbidity rates for the diseases mentioned during the current winter (1943-1944) in comparison with those for the previous winter. It will be noted that during the months of November, December, and January of the current winter the rates were considerably higher than for the corresponding months of the previous winter. This relation was reversed in February, when the sulfadiazine program was in progress for 21 out of 29 days, and this reversal was most pronounced in March, when the program was in effect for the entire month. During this period there were no changes in the general health program of the station, no improvement in housing facilities, and no reason other than sulfonamide to which the decrease in morbidity might be attributed.

Chart 44 shows the rates for scarlet fever and for rheumatic fever during the past winters. It is again evident that the incidence of these two diseases, both of which provide an indication of the incidence of streptococcal infections, was higher by a wide margin during the early months of the current winter than in the corresponding months of the preceding winter. In the light of the previous winter's experience, there was every reason to expect a high incidence for both diseases in March, 1944; however, the rates for both diseases fell to a lower level in March, 1944 than in the previous March and in the preceding months of the current winter.

Chart 45 shows the morbidity from respiratory diseases at the Navy Pier and at five other Naval activities in Chicago. The average strength for the Navy Pier during the period studied is approximately that of the other activities combined. Although these other groups are not entirely comparable to the group at Navy Pier, all these activities are training schools with a turnover of personnel between 3½ weeks and 4 months, and all are located in an area where respiratory infections have been particularly prevalent during the period of observation. The morbidity rates of these activities, therefore, serve as an indication of the month-to-month trend in the incidence of respiratory diseases in Chicago. It is seen in chart 45 that the incidence of these diseases during February and March fell only at the Navy Pier. In March, the first full month of sulfadiazine prophylaxis, the incidence of respiratory disease at the Navy Pier was by far the lowest of any naval activity in Chicago.

Summary

1. The incidence of respiratory tract infections was high at the Navy Pier in the winters of 1943 and 1944.

2. In January, 1944 streptococcal infections at the Navy Pier seriously handicapped this activity and gave rise to a high incidence of rheumatic fever.

3. The institution of sulfadiazine prophylaxis was followed by a prompt fall in the rate of respiratory infections, including scarlet fever, and a progressive fall in the incidence of rheumatic fever.

4. In March, 1944 when the incidence of respiratory disease, scarlatina, and rheumatic fever was high at Naval activities in the Chicago area, it was minimal at the Navy Pier.

5. This precipitous decline in the incidence of these diseases during February and the maintenance of these low rates during the spring months at Navy Pier is attributed to the effectiveness of sulfadiazine in preventing bacterial infections of the respiratory tract.

6. The incidence of drug reactions was 0.188 percent in February and 0.375 percent in March. About 40 percent of the men retested were found sensitive. No severe reactions occurred.

Conclusion

Mass Chemoprophylaxis
The U. S. Navy's Six Months' Program for the Control of Streptococcal Infections

Commander Alvin F. Coburn (MC)V(S), U.S.N.R.

Altogether throughout this program more than 600,000 Naval trainees received daily doses of sulfadiazine to protect them from respiratory diseases. The results of 6 months' observation permit an appraisal of this prophylactic measure. Before attempting to weigh the advantages and disadvantages of this strategy for attacking respiratory pathogens, one must first understand the nature of the problem at the Naval training activities that instituted this Streptococcal Control Program.

The Problem

A high morbidity rate for hemolytic streptococcal infections occurred in the U. S. Navy during the first quarter of 1944. The distribution of Naval activities with a high incidence* of diseases believed to be of streptococcal origin is shown in charts 46, 47, and 48 in which are indicated stations that had an extremely high, a moderately high, or a high disease rate for several weeks of the winter months.

The distribution of scarlet fever was similar to that of tonsillitis and pharyngitis. High rheumatic fever rates occurred where the rates for one or all of these respiratory diseases were high. The Thirteenth and Ninth Naval Districts consistently showed the highest morbidity rates for all these infections throughout January, February, and March of 1944.

No two stations had identical or, with one exception, even similar problems:

* Data obtained from weekly morbidity rates expressed in annual admission rates per 1,000 strength.

1. At Farragut, respiratory diseases had proved a menace in 1943. Strains of hemolytic streptococcus had acquired an alarming degree of pathogenicity. The micro-organism appeared to be almost as communicable as respiratory viruses. At one time 8 percent of all personnel were on the sick list because of streptococcal diseases. In one year, hemolytic streptococcus had precipitated about 5,000 cases of scarlet fever and 1,500 severe rheumatic attacks. Its virulence was maintained during the summer months and within a few weeks after the onset of winter, there were more than 200 cases of primary streptococcal pneumonia. Its activity in these patients and in those developing rheumatic fever was followed by a high incidence of incapacitating disease. The problem was to check the epidemic process quickly, so that this station might continue to function.

2. At Great Lakes, strains of hemolytic streptococcus had caused a tremendous loss in man-days during the winter and spring months of 1943. With increasing numbers of personnel in training, there were good indications that the morbidity rate as a result of respiratory diseases would increase throughout the winter and spring months of 1944 unless measures were instituted to control scarlet fever, tonsillitis, and rheumatic fever.

3. At Sampson, hemolytic streptococcus had manifested great activity shortly after the opening of the station. The pathogenicity of the micro-organism apparently subsided during the summer months. The objective was to prevent any strain from acquiring virulence.

4. At Davisville, hemolytic streptococcus had not proved to be a menace; however, the station is situated on the New England coast where streptococcal infections are likely to occur. The problem there was to prevent the entry of hemolytic streptococcus.

5. At Bainbridge, several serologic types of hemolytic streptococcus had manifested varying degrees of pathogenicity during the spring months of 1943. Type 19 regained considerable activity in the fall months. The problem there was to suppress this micro-organism which had spread throughout the station.

6 and 7. The Naval Air Technical Training Centers at Norman and Memphis were severely crippled by streptococcal infections in December 1943 and January 1944 when vicinal Naval and civilian activities were having exceptionally low streptococcal morbidity rates. Both of these stations had experienced epidemic influenza in the fall months of 1943 and this had been followed by serious streptococcal infections. About 6 percent of all personnel were on the sick list in January, and primary streptococcal pneumonia with its suppurative complications had made its appearance. The problem at each of these stations in January 1944 was to check an epidemic caused by highly virulent strains of hemolytic streptococcus.

THE DISTRIBUTION OF U. S. NAVAL ACTIVITIES WITH HIGH MORBIDITY RATES FOR SCARLET FEVER IN THE WINTER OF 1944

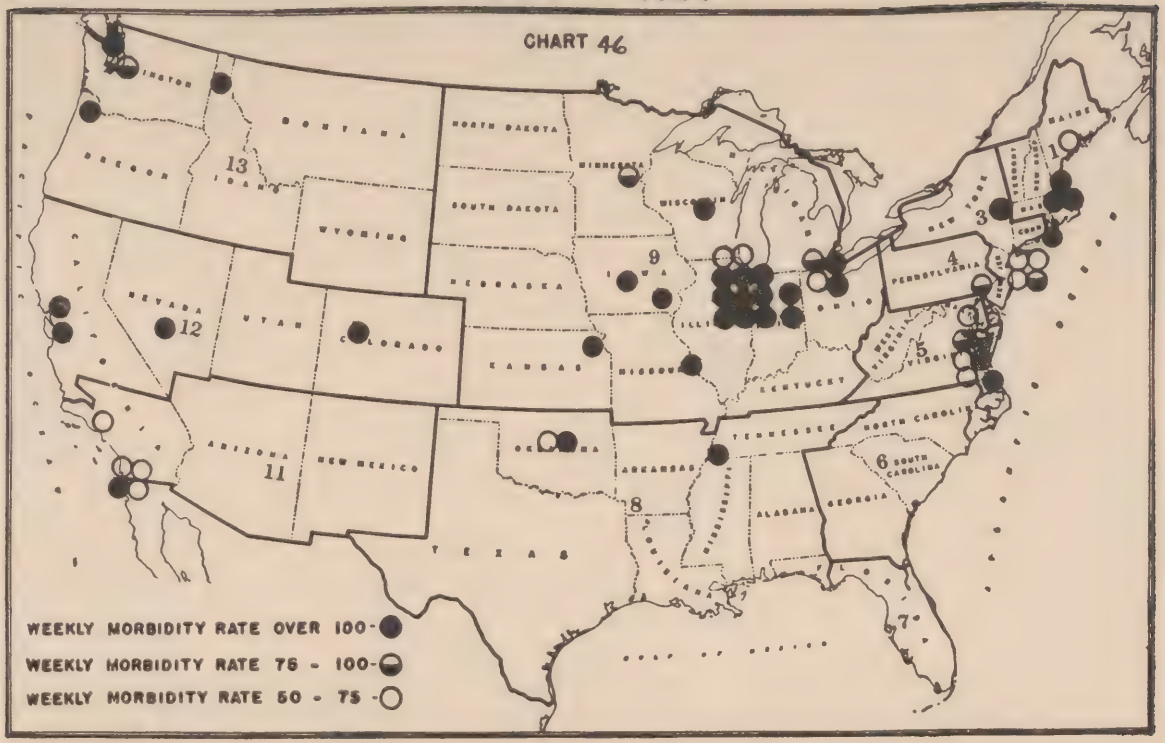


CHART 46

THE DISTRIBUTION OF U. S. NAVAL ACTIVITIES WITH HIGH MORBIDITY RATES FOR PHARYNGITIS AND TONSILLITIS IN THE WINTER OF 1944

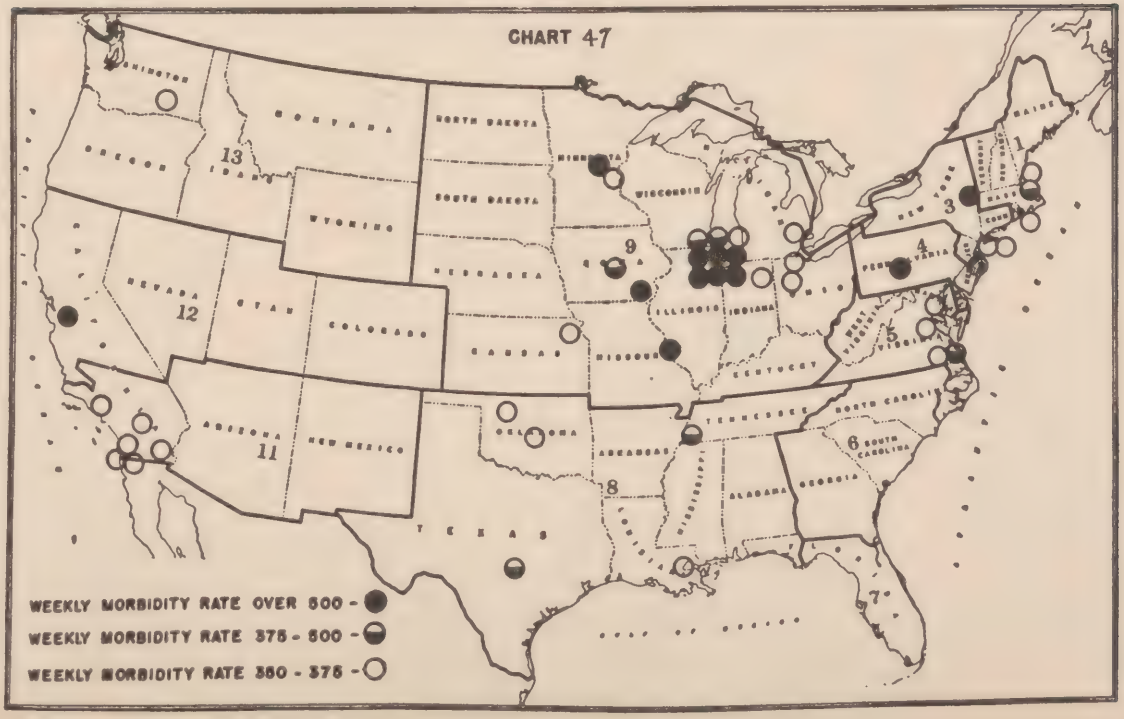
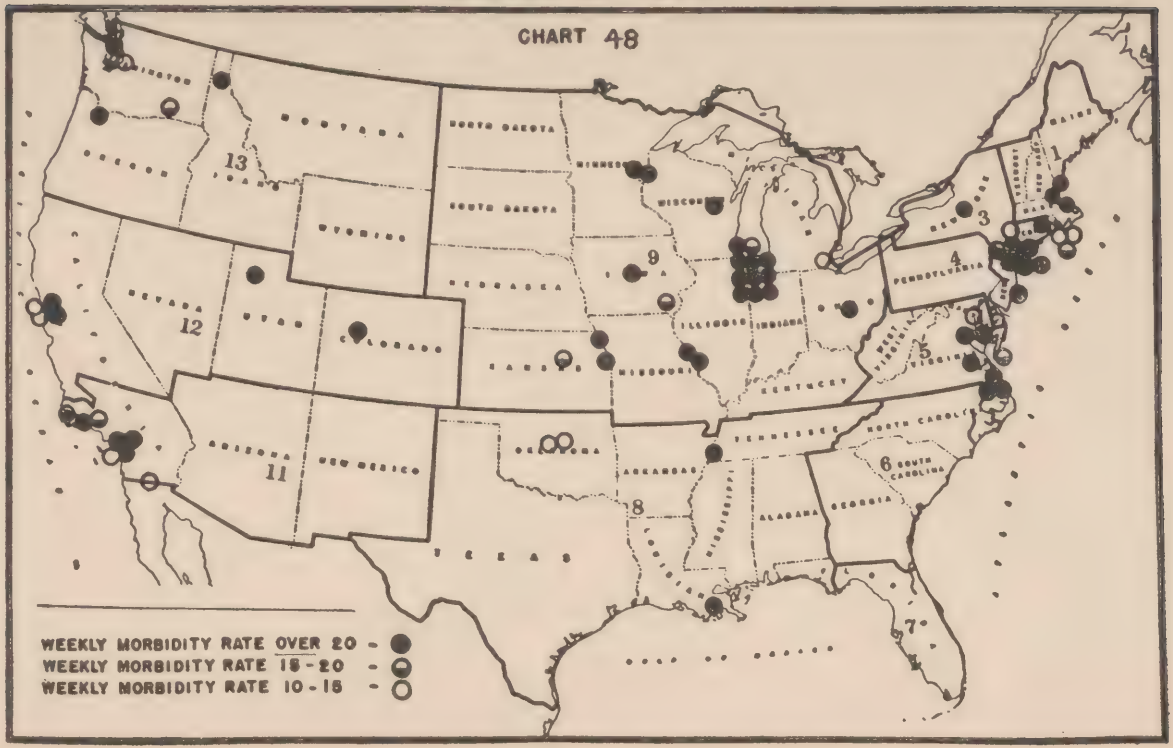


CHART 47

THE DISTRIBUTION OF U. S. NAVAL ACTIVITIES WITH HIGH MORBIDITY RATES FOR RHEUMATIC FEVER IN THE WINTER OF 1944



8. At Navy Pier, Chicago, the training of personnel had become seriously handicapped in December 1943. That station had experienced a high incidence of streptococcal infections in previous winters with subsequent high rheumatic fever rates. Late in 1943, it appeared that pathogenic strains had become exceptionally active prior to the onset of winter. During December 1943, more than 25 percent of the station's complement were admitted to the sick list because of respiratory infections. The objectives of prophylaxis at that activity were to check a well advanced streptococcal epidemic and to prevent the implantation of other streptococcal strains during the spring months of 1944.

Hemolytic streptococcus, although the most important, was not the only respiratory pathogen causing concern at those several stations. Meningococcus had caused an epidemic at Davisville, and fulminating, fatal disease at other activities. Pneumococcus had been the causative agent in most of the cases of pneumonia at stations that experienced cold winters. Gonococcus had caused considerable morbidity among groups who had finished "boot" training and rated liberty.

Factors in the Pathogenesis of Respiratory Epidemics at Naval Training Centers

Five conditions favoring the development of respiratory epidemics were satisfied at each of these training centers: (1) Fresh, highly susceptible recruits were introduced almost daily; (2) there was a high rate of change in population during the program for rapid training; (3) overcrowding and the congestion of large numbers of men in sleeping quarters occurred; (4) outbreaks of influenza or measles developed either prior to or during the prophylactic program; (5) most of the training centers were seeded with strains of respiratory pathogens which had already shown extreme communicability.

Other less obvious factors, which varied from station to station, were also operative. At some, high temperatures with extremely low humidities were maintained in the barracks during the winter months. At others, dust storms presented a serious local problem. Rapid fluctuations in outdoor temperatures, rain, snow, fog, and other climatic states were variables at each activity. Many of these conditions, not subject to appraisal, were unfavorable to the normal, physiologic responses of the host, and, therefore, were favorable to the invasion of bacterial respiratory pathogens.

It was possible to anticipate that respiratory pathogens would be prevalent at Naval training activities in times of war; nevertheless, preventive medicine has not yet mobilized the forces necessary to prevent a high incidence of communicable diseases during the rapid expansion of training programs. The reasons are obvious: Training large numbers of recruits with inadequately developed facilities precludes the execution

of well established principles of good hygiene, and there are many factors inherent in the pathogenesis of these diseases to be controlled.

The significance of some of these modes of infection is becoming more and more apparent:

1. The contamination of meat and milk has long been recognized as a cause of explosive outbreaks.

2. The direct transmission of respiratory pathogens from infected persons during the incubation and convalescent states is accelerated by overcrowding and billeting in times of war. The use of double-decked bunks permits the direct transmission of large inocula of bacteria from man to man.

3. The possibility of insufflation of infected particulate matter occurs with intensive recruit training in swimming. One man plunges into the water of a pool and contaminates it with purulent exudate from the nasal sinuses or the respiratory tract. This material, uninfluenced by short exposure to chlorine, may be forced under pressure into the ears, sinuses, or respiratory passages of the recruits who follow in quick succession. The chlorination of swimming pool water may give little protection under these conditions, although affording a satisfactory bacterial count on analysis. Furthermore, chlorine acts as an irritant to the mucous membranes of many persons. This may be one of the several factors in swimming which lower the resistance of mucous membranes and increase susceptibility to the invasion of bacterial pathogens already harbored.

4. Indirect transmission of air-borne respiratory pathogens is tremendously accelerated by rapidly expanding training programs. Dangerous carriers of hemolytic streptococcus are barracked with fresh susceptibles. Floors and blankets are heavily contaminated with highly pathogenic organisms. Barracks are filled with new trainees as soon as billets become empty. Dust and blanket lint containing millions of organisms are disseminated with each cleaning of the decks and manipulation of blankets. The rapid turn-over of recruits and the failure to recognize the importance of dust control measures permit ideal conditions for the inhalation of small numbers of respiratory pathogens by large numbers of trainees. If these trainees are recruits, their susceptibility is further increased by a coincident lowering of resistance associated with acclimatization, changes in living conditions, and reactions to active immunizations against tetanus, smallpox, yellow fever, typhus fever, and enteric infections.

5. The indirect transmission of air-borne respiratory bacterial pathogens is further accelerated by the passage, directly or indirectly, of certain viruses. Measles and influenza are air-borne infections disseminated with facility in crowded barracks. Irrespective of whether an individual recruit contracts or escapes these virus infections, there can be no doubt that one of the final effects of virus activity in a Naval train-

ing center is increased pathogenicity of the prevalent strains of hemolytic streptococcus. With increased pathogenicity of this bacterium, the morbidity rate rises. The rise is followed by increasing dissemination which initiates the epidemic process.

Theoretically, it is possible to break this circle of spreading contagion, because methods are available to control each factor in the initiation and perpetuation of a respiratory epidemic. Medical science has almost eliminated the explosive outbreaks caused by the ingestion of food infected with hemolytic streptococcus. Careful screening out of convalescents before return to duty and elimination of double-deck bunks will reduce the incidence of "return cases" in which infection had been directly by the inhalation of infected droplets. The institution of technics for dust control, such as oiling of the decks and blankets in barracks, will reduce the incidence of indirectly transmitted air-borne infections. The cessation of instruction in swimming pools will eliminate infections caused by insufflation. The suppression of measles by passive immunization will remove an important virus factor. The protection of a recruit from infection during the first 3 weeks of "boot" training, when he is being acclimatized and actively immunized, will increase his resistance at the time of maximum exposure to hemolytic streptococcus.

Practically, it is impossible to control all these factors while conducting a rapidly expanding training program. The future will undoubtedly see the necessary control measures applied in preventive medicine. The present must accept the fact that the dissemination and inhalation of air-borne respiratory pathogens is not yet controlled by sanitation methods in the Navy. The medical officer cannot prevent the seeding of micro-organisms; the rooting of these pathogens in the floor dust; the transplantation and growth of these infectious agents among his men; the branching of this epidemic process to other men in his barracks; but he can now check the fruition of an epidemic process by preventing implantation of respiratory pathogens in susceptible recruits. It was for this purpose that the heroic measure of mass chemoprophylaxis was employed by the U. S. Navy.

An Appraisal of Mass Chemoprophylaxis

The present reports, collected in this monograph, clearly indicate the effectiveness of mass chemoprophylaxis. Each report represents the observations and consensus of several medical officers. The data included come from the labors of hundreds of line officers, petty officers, and hospital corpsmen. The material was obtained from large Naval training activities in all Naval districts of the United States where streptococcal infections were prevalent. The design of the prophylactic program was blueprinted to meet the needs of these stations with their individual respiratory disease problems. The execution of each program varied

with the size, ability, imagination, and resourcefulness of the individual epidemiology unit. The serologic typing of hemolytic streptococcus was done under constant conditions in one laboratory. With this exception, each report includes variables patently beyond control; nevertheless, given one blueprint based on the fact that the presence of sulfadiazine molecules on the mucous membranes exerts a bacteriostatic effect on respiratory pathogens; given half a million men to protect; given one sulfonamide to administer, and given one objective—given all these factors, medical officers report one conclusion: The strategy of mass chemoprophylaxis is fundamentally sound.

The effectiveness of sulfadiazine prophylaxis is shown in these studies to be determined in part by the epidemic mechanisms that the drug encountered. For example, the pathogenesis of a meningococcal infection seems to depend on the spreading of this organism throughout a "herd"; the pathogenesis of a streptococcal infection seems to depend on implantation of a virulent strain in the susceptible host; the pathogenesis of a pneumococcal pneumonia seems to depend on the lowering of resistance of a carrier. The effectiveness of chemoprophylaxis varies accordingly:

1. Previous observations have indicated that so long as the carrier rate of meningococcus is kept low, cerebrospinal fever rarely develops. The presence of small amounts of sulfadiazine exerts such a highly bacteriostatic effect on meningococcus that the carrier rate is reduced to a minimum. Chemoprophylaxis has, therefore, proved to be perfect protection against cerebrospinal fever in these half million men.

2. Previous studies have also shown that sulfadiazine, either in prophylactic or therapeutic dosage, has little effect on the throat flora of carriers of hemolytic streptococcus. The present observations have proved confirmatory. They showed, moreover, that the presence of small concentrations of sulfadiazine in the nasopharyngeal secretions "screens out" hemolytic streptococcus. Implantation is prevented in most instances, irrespective of the pathogenicity of the prevalent strains; however, in some instances, it was shown that organisms penetrated the bacteriostatic effect of sulfadiazine. This occurred after a man had been ingesting 1 gm. of drug daily for a period of weeks and was maintaining a satisfactory blood level. This was observed in areas where the exposure to streptococcal infections was greatest, and especially among recruits receiving swimming lessons in the chlorinated water of pools. This occurred most strikingly at the time when the incidence of measles was high. There are these undefined conditions that permit hemolytic streptococcus to overcome the bacteriostatic effect of small amounts of sulfadiazine. As clearly indicated, however, the presence of sulfadiazine in the nasopharyngeal secretions usually prevents the implantation of a new strain of hemolytic streptococcus in the throat flora. By this achievement, chemoprophylaxis prevents about 95 percent of the frank streptococcal infections

and about 85 percent of the presumptive streptococcal infections and rheumatic fever.

3. Previous studies have also shown that mechanisms essential for the pathogenesis of pneumonia are different from those of meningococcal and streptococcal infections. A person may be a carrier of pneumococcus for many weeks and escape disease until an episode upsets the host-parasite balance in favor of the micro-organism. The present observations show that a considerable percentage developed pneumococcal lung infections and pneumococcal otitis media while maintaining a sulfadiazine blood level of about 2 mg. percent. One factor in the pathogenesis of these diseases may have been insufflation occasioned by swimming. Another factor, demonstrated in certain instances, was the prevalence of sulfonamide-resistant strains of pneumococci.

4. Previous observations have also indicated that there is variation in the resistance of strains of gonococcus to sulfonamides. The present studies indicate that in certain areas, especially among Negro recruits, chemoprophylaxis was about 95 percent effective and that in other areas, it was less effective. Although no effort was made to determine the application of small sulfadiazine doses administered on the day following exposure, the limited observations suggested that this procedure was ineffective.

Untoward Reactions

The administration of sulfadiazine prophylaxis to half a million men afforded the opportunity to observe most of the untoward drug reactions that occur. No renal complications were detected. Most of the reactions were dermal; they are described in detail in several of these reports. They occurred in about 0.5 percent of Naval trainees during this program. Two severe types of reactions, exfoliative dermatitis and granulocytopenia, occurred in about 0.01 percent of men receiving prophylaxis. These dangerous manifestations appeared to be reversible unless the patient was given therapeutic doses of sulfonamide. Twelve of the fourteen patients who died from one of these two diseases are known to have received sulfonamide therapy.

It was observed that a few exhibited drug reactions on the first day of prophylaxis. These usually gave a history of having previously experienced reactions following sulfonamide therapy. Most of the drug reactions developed, however, after a lag period of about 2 weeks, comparable to that of serum sickness. A few with severe drug reactions appeared to have sulfadiazine fixed in the tissues as evidenced by the recovery of the drug from bullae in the skin and in considerable amounts from the blood and urine several days after ingestion of the last dose. Although the mechanism of these untoward reactions is unknown, the present observa-

tions suggest that a small percentage of human subjects handle sulfonamide in an abnormal manner and become sensitized. They have a drug idiosyncrasy and manifest sensitization, irrespective of whether sulfadiazine is administered for prophylaxis or treatment. The fact that about half of those who had dermal reactions were able to continue prophylaxis after a recess of 2 weeks remains unexplained.

Value of Serologic Identification of Hemolytic Streptococcus

Careful serologic identification of 5,000 strains of hemolytic streptococcus obtained from 16 training centers has supplied information on the epidemic spread of this micro-organism. The results of typing in conjunction with clinical observations indicate how variable is the activity of any type of hemolytic streptococcus. In the winter and spring months of 1944, types 19 and 17 were most injurious to Naval trainees throughout the United States. The bacteriologic picture differed, however, at each of the large training centers and individual variations were observed at smaller stations. For example, at a small Maryland activity a severe outbreak of streptococcal infections, which precipitated an extraordinarily high incidence of rheumatic fever, was caused by types 14 and 3. A coincident outbreak at another small activity in Pennsylvania was caused by type 30. At Bainbridge, type 19, which had been active in this large station since its opening in 1943, remained the predominant strain throughout 1944. Type 18, which was rarely recovered elsewhere, was second in predominance. In contrast, no type of hemolytic streptococcus gained epidemic qualities at the large training stations in Sampson, New York, or Davisville, Rhode Island. Furthermore, among the camps of the Great Lakes Naval Training Center, there were at least five epidemic strains: Types 5, 17, 19, 3, and 1. Type 5, which manifested extensive activity at that station, was relatively rare at other stations. Finally, at the large training center in Farragut, Idaho, types 17, 19, 1, and 3 were epidemic strains. Of these, type 17 showed the greatest virulence for man observed in a quarter century and was found to be strikingly susceptible to sulfadiazine prophylaxis. All four epidemic types at Farragut appeared highly communicable. The arrival of Farragut trainees at other activities was followed by streptococcal infections and the throat cultures at seven centers which received transfer recruits from Farragut revealed that the predominant types were 17 or 19 and the second in predominance 1 or 3.

Serologic typing of hemolytic streptococcus helped the epidemiologist to understand his local problem throughout this program. It was the only available laboratory aid to understanding the transmission of streptococcal diseases throughout camps and from center to center. The streptococcal typing of organisms from these half million men clearly demonstrated that vagaries in the behavior of this bacterium cannot be

anticipated. The practical application of information obtained by typing must remain limited until technics for immunization prove successful.

Coincident Virus Infections: A Variable to Be Assessed in Mass Chemoprophylaxis

One of the reasons that makes accurate assessment of mass chemoprophylaxis difficult is the unpredictable activity of hemolytic streptococcus. A number of factors are recognized as contributory in the evolution of epidemic strains of this micro-organism. One of these factors, which is perhaps most important in Naval activities, is the prevalence of respiratory virus infections. The two most significant are influenza and measles viruses. In the Navy it has been possible to record with a fair degree of accuracy the activity of measles. The present reports support the clinical observations of World War I that the measles virus catalyzes the activity of hemolytic streptococcus. During the first 6 months of 1944, it was observed that in those large training centers where outbreaks of streptococcal infections occurred, they were either preceded or accompanied by epidemics of measles. Conversely, the large training centers that escaped an outbreak of measles, irrespective of the presence or absence of chemoprophylaxis, also escaped a high morbidity rate from streptococcal infections. The following examples illustrate this point:

1. Four large activities in New York, Rhode Island, North Carolina, and Virginia had almost no measles and almost no scarlet fever.

2. Three large training centers in southern California, Oklahoma, and Tennessee experienced contra-seasonal streptococcal epidemics in geographic environments where streptococcal diseases were rare. In each instance these epidemics either followed or accompanied outbreaks of measles.

3. At one large activity in Idaho the scarlet fever rate was low from October 1942 until April 1943. It then rose precipitously for 2 months, declined moderately from June to September, then rose moderately, and finally hemolytic streptococcus manifested its greatest pathogenicity in January of 1944. The initial appearance of the streptococcal process occurred at the same time that a measles epidemic of 2 months' duration was subsiding. The second outbreak accompanied an outbreak of influenza. The final epidemic of most severe streptococcal infections accompanied a second outbreak of measles.

It appeared in these studies that the occurrence of epidemics of measles or influenza in areas where hemolytic streptococcus was inactive was relatively harmless; but in areas where hemolytic streptococcus was already moderately active, these virus outbreaks were accompanied by severe streptococcal epidemics. In several instances, there was a lag of from 4 to 8 weeks between an outbreak of measles and the manifestations of a streptococcal epidemic. With the exception of one small college.

no streptococcal epidemics occurred at Naval activities in the winter or spring of 1944 which were not preceded or accompanied by an outbreak of measles.

These observations indicate that the activity of these two viruses in some way reinforces the communicability of hemolytic streptococcus. It is impossible to forecast the activity of respiratory viruses. And it is, therefore, impossible to predict with accuracy where and when streptococcal epidemics will occur. Whether the extremely low streptococcal morbidity rates at two centers can be attributed solely to chemoprophylaxis in the absence of measles and influenza during these winter months remains to be determined. It is possible, however, to conclude from these reports that sulfadiazine is highly effective in preventing the implantation of hemolytic streptococcus in the upper respiratory tract of susceptible groups of recruits living in camps heavily infected with measles and pathogenic strains of hemolytic streptococcus.

Sulfonamide Resistance of Hemolytic Streptococcus: A Potential Variable in the Effectiveness of Mass Prophylaxis

Sulfadiazine prophylaxis was not 100 percent effective in preventing the implantation of hemolytic streptococcus. Some strains were able to infect those who had ingested 1 gm. of sulfadiazine daily and who maintained a blood level of 2 mg. percent. The explanation for this phenomenon is not yet known. It has been suggested that these persons may have inhaled a heavy inoculum; may have been infected by direct contact; may have had a low concentration of sulfadiazine in the secretions of the respiratory tract; or may have insufflated during swimming purulent water containing living micro-organisms and cellular débris which acted as a sulfonamide inhibitor and afforded protection to the respiratory pathogen. These possibilities are real; however, another possibility which may be of greater significance is the resistance of the micro-organism to prophylactic doses of sulfadiazine.

That no sulfonamide-fast strains were encountered during this program is shown by the fact that those who contracted streptococcal infections while receiving prophylaxis responded satisfactorily to therapeutic doses of sulfadiazine. That sulfonamide resistance did not develop generally is shown by the fact that there was no increase in streptococcal morbidity throughout 6 months of prophylaxis. The typing results of May 1944, suggest, however, that type 19 may have developed resistance to small concentrations of sulfadiazine. During this final month of the program, type 19 became the predominant organism at several Naval activities. At one activity, where all hands received prophylaxis, the predominant type disappeared and type 19 was the causative agent in virtually all respiratory infections.

Final solution of this problem has awaited the development of an "inhibitor-free" medium which will support normal growth of all strains of group A hemolytic streptococcus. Such a medium has recently been developed in the Typing Laboratory of the National Medical Center at Bethesda, and appropriate studies are now being made to determine whether strains recovered after 6 months of prophylaxis are more resistant to sulfadiazine than strains recovered and frozen at the onset of this program. A final opinion will be forthcoming with the results of these cultural studies. At present, the possibility that some strains of group A hemolytic streptococcus are resistant to 1 mg. percent of sulfadiazine in the secretions of the respiratory tract seems actual. This may well be the most important factor in limiting the effectiveness of sulfadiazine prophylaxis in preventing implantation of group A hemolytic streptococcus.

Summary

1. One cannot estimate accurately the saving in dollars, man-days, or lives which results from chemoprophylaxis.

2. The observations made at eight Naval training centers indicate that chemoprophylaxis is 85 percent effective in preventing bacterial infections of the respiratory tract under conditions favorable to the dissemination of respiratory pathogens and unfavorable to newly inducted recruits.

3. In these groups of Naval personnel, a saving of a day per man, per month, can be expected when bacterial respiratory pathogens are active. If the center's recruit complement is 30,000 and all hands receive sulfadiazine prophylaxis, one can anticipate a saving of 30,000 hospital days each month during seasons conducive to respiratory diseases. This is equivalent to freeing a 1,000 bed hospital and all the labor and personnel associated with the care of the sick.

4. These reports indicate the many assets and the few disadvantages of mass chemoprophylaxis.

These observations are presented by the Bureau of Medicine and Surgery of the United States Navy during this period of national crisis in the hope that they may prove a help to the Armed Services, an asset to the economy of a people at war, and an advance to the progress of medicine after the establishment of peace.

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